Transcript of October 17, 2001 Meeting

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CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

Executive Committee Meeting

October 17, 2001

Centers for Medicare and Medicaid Services

7500 Security Boulevard

Baltimore, Maryland

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Panelists

Chairperson

Harold C. Sox, M.D.

Vice-Chairperson

Robert Brook, M.D.

Voting Members

Leslie P. Francis, J.D., Ph.D.

John H. Ferguson, M.D.

Robert L. Murray, Ph.D.

Alan M. Garber, M.D., Ph.D.

Michael D. Maves, M.D., M.B.A.

Joe W. Johnson, D.C.

Thomas Holohan, M.D.

Daisy Alford-Smith, Ph.D.

Wade Aubry, M.D.

John Ferguson, M.D.

Barbara McNeil, M.D., Ph.D.

HCFA Liaison

Sean R. Tunis, M.D., M.Sc.

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Panelists (Continued)

Consumer Representative

Linda A. Bergthold, Ph.D.

Industry Representative

Randel E. Richner, M.P.H.

Executive Secretary

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PANEL PROCEEDINGS

(The meeting was called to order at 8:50 a.m., Wednesday, October 17, 2001.

MS. ANDERSON: Good morning and welcome, Committee chairperson, members and guests. I am Janet Anderson, Executive Secretary of the Executive Committee of the Medicare Coverage Advisory Committee, known as MCAC.

The Committee is here today to discuss and vote upon the findings of the Diagnostic Imaging Panel regarding the diagnosing and staging of breast cancer using Positron Emission Tomography scanning technology, or PET; discuss and vote upon the findings of the Drugs, Biologics and Therapeutics Panel regarding the use of levocarnitine injections for end-stage renal disease patients.

The following announcement addresses

conflict of address issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interests. To determine if any conflict existed, the Agency reviewed all financial interests reported by the

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Committee participants. The Agency has determined that all members may participate in the matters before the Committee today.

With respect to all other participants, we ask that in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees, and significant institutional support.

And now I would like to turn the meeting

over to Dr. Sean Tunis and then to Chairman Dr. Harold Sox who will ask the Committee members to introduce themselves and to disclose for the record any involvement with the topics to be presented today.

DR. TUNIS: Thanks, Janet. I just wanted to briefly welcome all of the Executive Committee members as well as the guests who are attending. Executive Committee members, we really appreciate your willingness to come to each of these meetings and provide your input, feedback and advice. The only thing I wanted to mention, the question has been asked to me again today whether

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this is the last time the Executive Committee will be considering the recommendations made by a panel on a specific coverage issue, and as I mentioned in the past, the BIPA law passed last year, Benefits Improvement and Protection Act, did go into effect October 1st, or some pieces of it, and one part of that legislation was intended to remove the ratification function from the Executive Committee.

There were some minor drafting problems in that legislation which makes it unclear as to whether in fact your ratification function has been removed and we're working on clarifying that language, so for the time being, there is one scheduled panel meeting coming up before the next Executive Committee, that's I believe January 10th, the Diagnostic Imaging Panel will be meeting to talk about use of PET for Alzheimer's disease or suspected dementia, and the Executive Committee will be meeting again after that and whether or not you do or don't ratify or consider ratifying that recommendation will depend on what happens in terms of technical corrections for the legislation. So I hope that is extremely clear, you either will or you won't.

DR. BERGTHOLD: Yeah. If we do, will it make it better?

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DR. TUNIS: So with that, I'd like to hand the meeting over to Dr. Sox and we will proceed with the business.

DR. SOX: Thank you very much. We have I think a fairly straightforward agenda today and look forward to the discussion this afternoon about a number of unrelated items about how we as the Executive Committee function.

I would like to start off by asking each of the members to introduce themselves, and if you have had any prior engagement with questions that we're going to be discussing, and that could be either financial conflict or it could be simply an intellectual engagement if you've written an editorial or something like that on the subject, I think we need to hear that, and conceivably but probably not recuse you from voting on the basis of that. So please be sure to let us know not only about your potential financial conflicts, but also any intellectual conflict.

So, with that as introduction, Joe, could you start by introducing yourself?

DR. JOHNSON: Joe Johnson, Paxson, Florida, private practice chiropractic, no conflict.

DR. MCNEIL: Barbara McNeil, Harvard

Medical School Health Policy and Radiology. I'm a member of the Blue Cross TEC panel which reviewed the original assessment on PET and breast cancer.

DR. MAVES: Mike Maves, Consumer Healthcare Products Association. No conflicts.

MS. RICHNER: Randel Richner, Boston Scientific. No conflicts.

DR. FERGUSON: John Ferguson, consultation in healthcare. No conflicts.

MS. BERGTHOLD: Linda Bergthold, consumer representative. No conflicts.

DR. SOX: Just before Dr. Aubry introduces himself, I would like to introduce him as the newest member of the Executive Committee, now the vice chair of one of the panels, and by virtue of that is a member of the Executive Committee, so welcome, Wade.

DR. AUBRY: Thank you. I'm Wade Aubry from the University of California at San Francisco, and I am vice chair of the Medical Devices Panel. I was formerly the chairman of the Blue Cross/Blue

Shield Association's TEC medical advisory panel which reviewed PET in the past. Otherwise, no conflicts.

DR. FRANCIS: Leslie Francis. I am in the law school and philosophy department at the University of Utah and I have no conflict or prior

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engagements.

DR. HOLOHAN: Dr. Tom Holohan. I am chief of patient care services for the Veterans Health Administration. No conflict.

DR. GARBER: Alan Garber, with the Department of Veterans Affairs and Stanford University. I also serve on the Blue Cross/Blue Shield Association's medical advisory panel and have reviewed PET in that context. I have also written about PET when used for myocardial perfusion imaging.

DR. ALFORD-SMITH: Daisy Alford-Smith, director of the Summit County Department of Human Services in Ohio, and I have no conflict.

DR. MURRAY: Bob Murray, Advocate Healthcare in Chicago. No conflicts.

DR. SOX: I'm Hal Sox, editor of Annals of

Internal Medicine, no conflict or prior engagements. So, with that we will begin and we're going to hear first from the imaging panel, and Barbara, are you going to present in Frank's absence?

DR. MCNEIL: I am, thank you.

DR. SOX: Good.

DR. MCNEIL: Sox. As Hal mentioned, I am standing in Frank's shoes here and he has a summary which he prepared, but what I would like to do is do

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it a little bit differently and actually present a quick number of slides to make it easier as we go along to show you the things that we addressed, as well our results. I would encourage you not to try to match up the language I'm using with the slides, because they are slightly different, but the content is the same.

What we are going to be discussing here are our deliberations on PET for the diagnosis and staging of breast cancer. When I give you the results on the subsequent slides, they were all

unanimous except for one, and I will tell you about that when we get there.

On June 19th we heard a presentation of the Blue Cross/Blue Shield TEC assessment by a staff member of the association. We had scheduled commentary from three individuals shown here. We had open comment from several individuals shown here, and they were either representatives of consumer organizations, currently practicing, or representing themselves or their field.

And in the course of the day we had a considerable amount of interaction back and forth between the panel and the commentators. It is important to note that following the scheduled

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presentation, scheduled commentary, there was considerable interaction back and forth.

So, I'm going to run through the questions that we addressed, and you have the full report, I am not going to go through all the data, that would take up all day, so I'm going to give you the questions, the results, and one or two pieces of data that led

to our decision.

So the first question was, is there adequate evidence that PET can improve health outcomes when used to decide whether to perform a biopsy in patients with an abnormal mammogram or palpable mass, and the issues here were very straightforward. There were 13 studies and the decisions came down to two parts. One is, the data did not extrapolate for individuals who had a low probability of having a malignant mass, and therefore it was not possible to use the published data to make a decision regarding the low probability individuals. And then on the other side of the coin, the false negative rate of the associated studies was high enough that it precluded the use of this procedure for patients with a high suspicion lesion. So, we voted negative unanimously.

The next question was, could PET be

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helpful in determining which patients should be biopsied right away versus which patients should be

followed up. So the question is, is there adequate evidence that PET can improve health outcomes by leading to an earlier and more accurate diagnosis of breast cancer compared to a short-term follow-up in patients with low suspicion lesions? And the answer here was quite clear, there were no data. And when I say no data, I mean no convincing scientific data; there may have been a case report or two, but there was nothing significant.

The next question had to do with a very important one and that involved whether PET improves health outcomes with regard to the decision to perform axillary node dissection, since this is a very important triage point in decisions regarding treatment for these patients. And here the data came down as follows: There was a meta-analysis of studies that showed that the true positive rate across all the studies in the field was about 80 percent, and the true negative rate was 89 percent, with a false positive or negative of about 11 percent.

And looking at the typical prevalences of

disease positive nodes, prior possibility of having

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diseased nodes in these patients, it is quite clear that with those sensitivities and specificities, there would be a high risk of undertreating patients with positive nodes using PET as a triage modality, so again, this was voted down unanimously.

Next we moved to this question, is there adequate evidence that PET improves health outcomes as either an adjunct to or replacement for standard staging tests in looking for locoregional recurrence or distant metastases. And when we looked at that question, we really thought that the question as written lumped two concepts that we had a hard time dealing with. And in the course of the deliberations within the panel and the discussion of those who commented on the analysis and some guest analysis, we decided to split the question into two parts.

So we first considered whether PET could be used in following up patients after they had been diagnosed and after they had been treated for breast

cancer, and use PET as a replacement for standard imaging modalities looking for disease recurrence, and we again concluded that there were no data, so that resulted in a negative vote.

Another question came up, well, what about as an adjunct, suppose there is a patient with breast

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cancer and the physician is looking for recurrent disease after treatment, and is quite sure or is reasonably certain that there is recurrent disease, what about PET as an adjunct to existing modalities when that decision needs to be made. This one generated quite a lot of discussion, I would say at least an hour, and the results of the deliberation shown there is we voted affirmatively with one abstention.

And the reason for the vote is shown here. We had two published studies in which the data were adequate to show that PET could be used as an adjunct to existing modalities. That's basically the all else fails approach. The committee felt as a result of the discussion that PET might be helpful in this

particular clinical situation and therefore, had this split vote. It was a very close call, throughout the discussion, and clearly the vote could have gone either way to be honest, as indicated by the one abstention, which could have been a negative vote, so I want you to understand that it was a close call. And then the final question was what about using PET to evaluate tumor response to different kinds of chemotherapeutic agents so that the referring clinician would know whether to continue

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the patient on that particular modality of therapy or to stop it and to switch to something else. Obviously in that kind of situation, the characteristics of the synergy modality have to be quite good because patients are either going to stop or get switched. And we all agreed that it was probably, of all of the things that we talked about, the most promising and important aspect of the use of PET from a clinical perspective, but the data were really

missing and they were missing from three perspectives. First, the studies are inadequate. Secondly, old, and old in the sense, not that they were published in the 1930s, if just that they could have been published recently but with chemotherapeutic agents that are irrelevant because they are no longer used, so in that regard it was not possible to consider them. And the third reason we gave for our decision was the fact that the longitudinal follow-up of the patients wasn't complete, so that patients dropped in and out and therefore, it was never clear what the denominator was for establishing specificity. Our bottom line was because of those three indications and because of the preliminary data from these inadequate, old and

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poor studies, even with those caveats, that there would be a fair amount of risk of undertreating patients or withdrawing them from therapy when that should have been continued.

So our request is that you ratify these recommendations made by the Diagnostic Imaging Panel.

That's it, I will be happy to take any questions.

DR. SOX: We will proceed now to scheduled public comment and will give anybody in the room a chance to stand up and comment, and then the panel has a good long period of time to discuss these recommendations before taking a vote. I believe we have one scheduled speaker, and if you could identify yourself and let us know who you work for.

DR. CONTE: My name is Peter Conte, associate professor of radiology --

DR. SOX: And if you have any conflicts or prior engagements to report, I hope you will do that.

DR. CONTE: Peter Conte, associate professor of radiology at University of Southern California. I have been federally sponsored as well as sponsored by the public and private sector firms for conducting research in the area of PET technology as well as clinical applications, so those are my

broad conflicts.

Good morning, Mr. Chairman, members of the Executive Committee, and ladies and gentlemen of the community. On June 19th I appeared on behalf of the Society of Nuclear Medicine and the American College of Radiology, representing a combined membership of over 42,000 professionals dedicated to providing high quality diagnostic and therapeutics services, and made a presentation to the Diagnostic Imaging Panel on the utilization of PET in breast cancer, and that is available as an attachment.

The presentation focused on new studies that were to be presented the following week at SNM's annual meeting in Toronto, Canada. At that time SNM and ACR urged the panel to approve the use of PET at the discretion of the referring physician in the diagnosis of known or suspected recurrent or metastatic disease for purpose of restaging patients with breast cancer. After due deliberation, the Diagnostic Imaging Panel voted affirmatively in response to the following question: Is there adequate evidence that PET improves health outcomes as an adjunct to standard staging tests in detecting

locoregional recurrence or distant metastases in recurrence when results from other tests are

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inconclusive. That's available in the minutes of the June 19th meeting and as you just heard.

Today as we enter the next phase of discussions, the positions of the ACR and the Society of Nuclear Medicine remain unchanged on this issue. We trust that this committee will agree with our professional constituency as well as the decision reached by your Diagnostic Imaging Panel and recommend Medicare coverage of this PET indication.

Now speaking as a member of the PET community at large, I would like to make reference to a recently published article that appeared in the September 2001 issue of the Journal of Nuclear Medicine, which I believe demonstrates our ongoing commitment to provide timely and relevant clinical data supporting the role of PET in the breast cancer population. A recurring question -- and by the way, this should not mean, we are not requesting an

extension of what we have done, we're just requesting that you listen to what our commitment is at this point.

A recurrent question during panel discussion on June 19th was whether the result of the PET scans change patient management. In this recent article, it was reported that a PET scan changed

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clinical management of 60 percent of women with recurrent breast cancer. It also changed the cancer staging of 36 percent of those scanned, and that's also available as an attachment in your packets. The study author, Johannes Churn from UCLA, found that results from 50 patients with breast cancer were reported by 32 different physicians in this survey. Clinical management changes, including moving from one type of treatment to another, for example from surgery to radiation therapy, or medical treatment to no treatment, other changes were within the existing treatment, changing from one kind of chemotherapy to another. The impact of the PET scan results was also significant on disease staging.

More than a quarter, 28 percent were upstaged and 8 percent were downstaged. Before the scan, 36 percent of patients were reported as having Stage IV cancer; after the scan, more than 52 percent were at this level as a result of finding previously undetected metastasis.

These results reinforce the importance of PET in making treatment decisions for women with recurrent breast cancer. Better treatment decisions should mean longer and better quality of life for those suffering from this disease. It seems

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particularly appropriate that during October 2001, National Breast Cancer Awareness Month, the Executive Committee of the Medicare Coverage Advisory Committee is presented with the opportunity to recommend coverage for FDG positron emission tomography for breast cancer. I again urge you support the specific decision made by the Diagnostic Imaging Panel this past June. I thank you for your attention and your thoughtful consideration.

DR. SOX: Thank you very much. Are there any questions that the panel members would like to address to the speaker? Barbara, maybe I could ask you if you could try to put what you reported, particularly this more recent study that I gather you didn't have a chance to review, into context for us.

DR. MCNEIL: Well, it does make me feel a little bit like a slouch, because I didn't read my September JNM yet, so I haven't actually read this article, so I really can't comment without reading the article, Hal, I don't think that would be right. I think it's not inconsistent with the recommendation that we made as an adjunct to, but I would not feel on the basis of what is written here that it should influence our decisions on the other

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recommendations at this point.

DR. SOX: It sounds like if anything, it's going to push us more toward an affirmative vote on the recurrent issue, but it's also true that we haven't had a chance to review the article and decide

whether the evidence in it justifies the conclusion the authors do.

DR. MCNEIL: Actually, I think that's an important point and I meant to make it during my remarks. During our deliberations in June, there were several other indications, or there was at least one other indication that was brought before the committee that was a possible question that we should have been addressing, and it involved the potential use of PET scanning for patients with dense breasts in whom the diagnosis of cancer is sometimes very difficult to make, and there was information presented by several people in the audience, mostly Dr. Gambhir from UCLA, who indicated that he thought that just intuitively, this would be the right thing to do, or a reasonable thing to do.

And the committee spent a long long time talking about whether we should make decisions on the basis of what hypothetically or theoretically might seem like a reasonable thing to do in the absence of

any underlying data to support that decision, so we made the decision that we should not do that. And I think if this supports the decision that we made, and I don't see any reason that it takes away from it, then I think we should go with our recommendations.

DR. SOX: One thing that the panel might want to discuss more procedural than anything else is its response to a report which starts moving us in the direction of better evidence but really stands in isolation, and what the proper response is under those circumstances. But I suggest we put that discussion off until we get into the panel discussion part of this presentation. So, any other comments? John.

DR. FERGUSON: Just that the question was posed is improving outcomes, and as I understand Dr. Conte, the article says changing management. And I would just comment that changing management is not the same thing as improved outcomes.

DR. SOX: Very good reminder.

DR. FRANCIS: I just have a question. I want to be sure I understand the logic. If PET is

used as an extra way to diagnose somebody with dense breasts when some other diagnosis isn't doing it, that's sort of logically like the way you separated

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the questions on recurrence, right? And I wanted to ask you whether anybody had raised the question of separating the question on initial diagnosis just as you did on diagnosis of recurrences.

DR. SOX: While Barbara is thinking about her answer to that, I just remind the panel members, please use the microphone so that everybody in the room can hear you easily.

DR. MCNEIL: The answer, Leslie, to that is no, because the original question dealt with a patient who had something on a mammogram, so the idea of PET would be to separate out the false positives from the true positives on the basis of the mammogram. The issue of PET as a screening modality basically came from the blue without any relationship to any of these questions, and I don't think it can be properly insinuated as part of these questions.

DR. SOX: Okay. Alan, do you want to raise an issue related to the scheduled public presentation or is this more for the general discussion period?

DR. GARBER: I'm just hoping we can get Barbara's slides back up for the general discussion.

DR. SOX: Yeah, we can. Let's try to stay on responses to the scheduled public presentation.

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MS. BERGTHOLD: I wanted to ask Dr. Conte whether the phrase at the discretion of the referring physician has any particular meaning. I don't see it anywhere else and it does appear in his testimony, and whether he was suggesting that, what does that mean basically? Tell us a little more about that.

DR. CONTE: Well, that's actually not -- that's what we requested earlier, but that's not the final language as you saw it that was shown on the slide. The final language does not include that phrase, so that's not what you're considering. But our intention at that time was that we would have the ability for the referring physician to interact with

the radiologist and nuclear medicine physician to make an individual treatment decision on a particular patient, so that there would be a need to do an additional test because there was some issue in that particular patient.

DR. SOX: Well, if there are no more comments, then we will go on to the second part, which is unscheduled open public comments. And do you wish to, and again, please identify yourself and state any relationships you might have that we ought to know about in order to interpret your comments correctly.

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DR. ADLER: My name is Lee Adler. I'm at Fox Chase Cancer Center and an officer on the Board of the Academy of Molecular Imaging, which was formerly known as the Institute for Clinical PET, which is the original petitioner to the former HCFA for this indication, and I am representing the AMI in making the statement that the AMI supports the positive recommendation of the advisory panel last

June to support the use of PET as an adjunct to conventional imaging in the evaluation of possible breast cancer recurrence.

I believe brevity is a virtue, so that's my statement.

DR. SOX: Thank you. Please.

DR. WAHL: I'm Richard Wahl, I'm director of nuclear medicine at Johns Hopkins, and I'm in the neighborhood. I'm also a member of the Academy of Molecular Imaging and past president of that organization, currently a member of the ACRS&M, consultant to a number of, well, at least honorarium from Siemens, who makes PET scanners, and GE who makes PET scanners, as well as PET-Net, who makes pharmaceuticals. The PET facility at Hopkins is part of nuclear medicine. I have written a book on PET and received royalties from that, and I think those

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are my major conflicts.

I wanted to just offer my personal support and also reiterate that of the AMI on the recommendation of the Diagnostic Imaging Panel from

June 19th. I had an opportunity to participate with that. I believe that the vote on the approved area was that it would be helpful, not that it might be helpful, and I think Barbara said might be helpful, and perhaps I misrecollected, but clearly that was a positive.

And I just wanted to mention that I had recently authored an article which just came out, actually came out in July, in Seminars in Roentgenology, it's called Current Status of PET in Breast Cancer Imaging, Staging and Therapy, and it's my review of the PET literature and it basically comes to a very similar conclusion as did the panel, and I have this available if anybody on the committee would like it, so I would encourage you to support the recommendation. Thank you.

DR. SOX: Good to hear from both of you, thank you very much. Would anybody else who's here like to comment before we go into committee discussion node? Any last chances to raise issues that you would like us to discuss?

In that case, we will now go into committee discussion mode, and I think we will in the interest of trying to be very open in this meeting, if people in the audience would like to put in their two dollars worth of comments as we get going, we will be happy to welcome that, try to stay as informal as we can without totally degenerating into an unstructured discussion.

So, Alan, could we first ask that Dr. McNeil's Power Point presentation --

DR. GARBER: Actually, from my question, Daisy pointed out we have a copy of the slides in our folders, so it's not essential, but I don't know the slide number, but it's the one that has the rephrased question on adjunct use. It says, is there adequate evidence that PET improves health outcomes as an adjunct, et cetera, affirmative. And then your next slide has adjunct data, two published studies, inadequate data. Discussions suggest that when all else fails, this might be helpful.

Now, I'm a little -- I'm not questioning

the conclusion, but I am, I guess I am questioning whether you can answer that yes, there is adequate evidence when you also claim that there is inadequate data. How did the committee reconcile these, getting

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to that conclusion, to that question when you also seem to have concluded there was inadequate data?

DR. MCNEIL: Alan, we had a terrible time. I mean realistically, it was one of the most difficult discussions I have ever been part of in trying to reach a conclusion that seemed to be reasonable. And in my mind there is no question that the data as presented to us and as written in the evidence report do not support this, they just are not there.

DR. SOX: Some of us were hoping the slides were going to remind us exactly what we're talking about.

DR. MCNEIL: Janet, could you put up, try number eight or nine.

So these two studies basically don't do it

realistically they don't do it, and in the course of the discussion, Dr. Wahl in particular brought up data that he had discussed in the article that he has passed around, and there were several clinicians there as well, and I actually can't remember who they are now, who suggested that this was a when all else fails approach, and that there were likely situations in which patients would be worked up with everything else that was available in which the suspicion of

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recurrent disease was high and therefore, PET might be useful in those circumstances, might or would, I'm not sure of which, but that it might be useful. But it was one of our most difficult questions and it was one of the ones that was least crisply defined in terms of the data, so I don't know, Alan. If we were to be making the decisions on the basis of the published data alone, it would be no, there is no question it would be no. I think we gave a little slack to the situation and maybe we shouldn't have, I don't know.

DR. SOX: Let me focus on that if I can

for a second. You said in patients where suspicion is fairly high, so if you didn't have a test, then you would do some direct approach like biopsy or --

DR. MCNEIL: If you knew where to biopsy, I think that was the idea. For recurrent disease you don't necessarily have any idea where to biopsy.

DR. SOX: But in patients where suspicion is high, high pretest probability, that's where diagnostic tests face the greatest challenge, because they have to have an extremely low false negative rate in order to, in order for a negative result to lower the probability of disease enough so that you could be confident you could sort of watch and wait,

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and you know, often a test with a sensitivity of 95 percent or better won't do it with a high pretest probability. Is there any reason to expect that the sensitivity of the test under these circumstances could be that high?

DR. MCNEIL: I don't know.

DR. SOX: Would you care to make a

comment, Dr. Conte?

DR. CONTE: Actually I would. I would like to make reference to an article by Peter Hathaway actually that discussed the issue of MR imaging of the axilla versus PET in patients with suspected recurrent disease, and I think it directly addresses this type of issue. And it was a small study, albeit 10 patients, but 50 percent of those patients had an equivocal MRI examination, but 100 percent of the lesions were detected on PET. So it's a good example of showing you where an inconclusive test such as an MRI to detect patients with suspected locorecurrence had failed and the use of an adjunct imaging test such as PET could come in, localize the lesion and then proceed on with the rest of the allegory, for example biopsy or surgical resection. So I think there is some data to support exactly the type of scenario that's being described.

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DR. SOX: So in these patients where the MRI was equivocal and PET identified a lesion, do these patients in fact have a cancer?

DR. CONTE: Yes, these were all surgical or biopsy proven. This is a small study, and you may have reviewed this in your original --

DR. MCNEIL: Yeah, actually, thank you, Peter. I had forgotten that that was one of the key examples that the audience brought to our attention. It was brought to us by Bahs Alavi from Penn, who talked about this clinical situation where there might be recurrence in the axilla and MR or CT, probably more likely MR were negative, and PET had turned out to be positive. I actually believe that has been the experience of the Farber in Boston. But again, this information is not well documented.

DR. SOX: It's again, a very small study, therefore, very wide confidence intervals on the estimate of sensitivity and a fairly high probability that the sensitivity could be considerably lower.

DR. MCNEIL: I think what Bahs was talking about was fewer than 15 patients, something like that.

DR. SOX: So if there were a hundred

patients and the sensitivity was still 100 percent,

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you would have much narrower confidence intervals and be much more confident that a negative test meant that nothing was there. Yes, please.

DR. WAHL: Richard Wahl again, from Johns Hopkins. Being at the June meeting, I remember one of the things we did discuss was the difficult situation of the patient who had had breast cancer and had had radiation therapy to the superclavicular and axillary region, and those are very difficult to examine on clinical examination and MR exams are very difficult because there's often gadolinium enhancement due to the radiation effects. In telling -- those patients often have pain and can have weakness in the arm, and it's very hard to tell if they have recurrent breast cancer or if they have just radiation damage to the nerves.

And PET, there were three articles referenced in that review I gave you, references 55, 56 and 57, all relatively small articles, but all showing the same thing, one of them being our

experience, that PET is much more reliable than contrast MR in determining if this tumor has recurred or not in that setting. Otherwise, you're stuck in a situation where the surgeon has to do blind biopsies of areas of MR enhancement which are often not

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clearly due to tumor. So the MR is probably 50 percent accurate in that setting.

These are small series, I agree, the confidence intervals are wide, but a lot of groups have seen this and I think several groups made the same comment at the meeting, and these settings in the soft tissues, especially after treatment, it can be exceedingly difficult to tell what's going on by standard diagnostic methods. Standard diagnostic methods work best when the anatomy is not altered. I mean, they look for symmetry and they look for normal tissue planes, but as soon as you have altered tissue planes, altered anatomy and altered contrast enhancement due to radiation, then you have all kinds of problems with standard imaging methods, and I

think that's where PET really excels in those difficult cases, at least in our experience.

DR. SOX: Thank you. Daisy, were you --

DR. ALFORD-SMITH: Yes, I did have a question. I am having some difficulty following and understanding the panel's recommendations, particularly if you use the slide that is currently there where you are recommending, or at least you voted in the affirmative with the understanding that there was a connection in improving health outcomes

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as an adjunct, when in fact it could not be used or seen as an adjunct just in determining whether to perform a biopsy.

DR. MCNEIL: I'm not exactly sure what your question is. Could you just rephrase it?

DR. ALFORD-SMITH: It appears to me that by voting in the affirmative on this particular one negates the negative that you voted on the previous ones, because it appears that it could be used at any time as an adjunct.

DR. MCNEIL: Well, the previous one was,

just to be clear, if I can be clear about what we were talking about was if a patient is suspected of having recurrent disease now with breast cancer, that individual can get a bone scan if the pain is in the bone, or perhaps an MR if they think it's likely, or CT recurrent in the soft tissues, they would get one of those tests, depending upon where the physician feels the disease has likely recurred. So this would be using PET as a replacement for.

And when we looked at the data that lined up patients who had CT, MR, bone scans and PET, or some combination of those in looking for recurrent disease, we couldn't really tease out from the data that PET had made a contribution that was positive in

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looking for recurrent disease over and above that which was seen by the imaging modalities alone, or in particular pairs. So that in our view was a clear-cut negative, a clear-cut negative vote, the data just weren't there.

This one, if anything, if we were to being

doing anything, we would say that the negative there made this a negative, rather than the positive here made that a positive. So, I don't know if that's what you're saying.

DR. ALFORD-SMITH: That's exactly what I'm saying.

DR. MCNEIL: Okay. So you're basically going pack to Alan's point that the negative vote on the replacement is absolutely clear, it's negative, there are no data to suggest that it can replace the other modalities. This one was, you've done them, you have this scarred neck or scarred axilla, patient's got arm pain, that was the example that was actually presented, and you just don't know why the patient has arm pain. And the MR as I recall in the case that was presented was kind of a mess because of the previous radiation therapy and they just couldn't see anything. So in that particular situation, nothing was working, and that's what we meant by

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adjunct to in a unique situation.

DR. SOX: I think -- I'm not sure who was

next, but why don't you go ahead, Leslie?

DR. FRANCIS: I just wanted to ask, in the argument there for why it changes patient management is not just a false negative versus false positive question but if PET shows you where to go, PET contributes additional information when you have a false negative on the one test.

DR. MCNEIL: Right. Now here you're getting way beyond my knowledge of the management of patients with recurrent breast cancer, way beyond, but I think the idea was if you actually found out, if it lit up in the axilla or the neck, you would know exactly where to go to biopsy, you'd do the biopsy and you'd find out it wasn't fibrosis, which was one possibility, but it was actually recurrent cancer. Somehow or other that triggers a treatment decision, and it's clearly not more radiation therapy, they have probably maxed out there, but it would be some kind of chemotherapy that they would try, I don't know the decision tree for the treatment there.

DR. SOX: Alan? Oh, before we go on, I would like a late arrival, Dr. Brook, and Bob, could

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you introduce yourself, state your affiliation and state any conflicts or prior engagements you might have had on the issues that we're going to be talking about carnitine deficiency in end-stage renal disease and PET for breast cancer.

DR. BROOK: Robert Brook from Rand at UCLA. The only conflict that I know about is that my mother, who was on Medicare, was referred to a PET scan for breast cancer, so that's the only conflict I have and I don't think that disqualifies me.

DR. SOX: Thank you. Sean, please?

DR. TUNIS: I just wanted to also mention for the committee that I just noticed walk in the room, we do have a card carrying oncologist, Ellen Feigal has joined us, she's somewhere in the audience, she's going to be speaking later. So if you have some questions about management of breast cancer and want to ask a real oncologist, she's probably not the only one in the room, but at least

she is here and I am announcing to her, now available for consultation.

(Laughter.)

DR. SOX: The doctor is in. Alan.

DR. GARBER: Well, Barbara, if I might take a little liberty with the language here, it

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seems to me that your panel would have felt comfortable, and correct me if I'm wrong, answering a question, does it appear likely that PET improves health outcomes as an adjunct? What you said in the next slide about the inadequate data, notwithstanding the other data we've heard about now, the panel had concluded, they wouldn't have had to struggle with this if they thought the data were adequate. Is that a fair statement?

DR. MCNEIL: Absolutely.

DR. GARBER: So, it seems to me the panel concluded the data were inadequate, notwithstanding the other studies we've heard about, and we could go into what these studies mean, and my interpretation

of what we heard is that there is a solid rationale to support the use of PET, but its implications for health outcomes may not have been fully worked out by the available literature.

DR. MCNEIL: That's correct.

DR. GARBER: And so therefore, the question that the panel addressed, it seems to me by our normal standards of adequate evidence, the panel's logic would lead to a negative on this, yet an affirmative on a closely related question of, do we think this is likely to be helpful. Would that be

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a fair statement of the point of view of the panel?

DR. MCNEIL: So we would change that to say, is it likely that PET improves health outcome.

DR. GARBER: Or does it appear promising, or language of that sort, because usually when we talk about adequate evidence we mean that the scientific basis is pretty clear, or clear enough that we feel comfortable concluding that it's established, and additional studies might be needed to refine some details, but basically the information

is in, and it doesn't seem that was the conclusion your panel reached.

DR. MCNEIL: No, actually that's a really terrific comment. I think if we did change it, it would reconcile the two slides and it would make Daisy feel better as well, it's clear the data aren't adequate, there's just no question about it, but there is a possibility that -- so, I'm the only one from the committee here, but I think that was clearly in the spirit of the decision or the recommendation by the committee.

DR. SOX: Another way to look at that is the panel is going to the point estimates for sensitivity and kind of willing to ignore the broad confidence intervals because statistically, you know,

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it's most likely that the point estimates will be the correct estimates when you get a bigger sample.

DR. GARBER: Well, Hal, actually I don't think that the sample size is the fundamental issue here. The sample size is one weakness of any study

that has ten subjects, but for all we know there may be many others, and I didn't review the many other weaknesses, biases, ascertainment bias, issues in how the patient populations were selected, and so I'm not saying these studies are guilty of that but a full review would have to account for that, and the panel which did review the data, Barbara is telling us, just did not feel they were adequate, and it could be for any number of reasons, not only sample size.

DR. SOX: I agree, point well taken.

Dr. Conte, if you'd like to comment, please step forward.

DR. CONTE: Peter Conte again, University of Southern California. I just want to also reiterate that I think the panel in our opinion from the public side was heavily swayed by clinical practice issues in addition to the literature, because there was a lot of discussion about the use of PET in specific situations and how it could change management.

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I also want to point out the fact that,

there was a comment made earlier about health outcomes versus altered management by one of the panelists, I don't remember who made the comment, but I think that's obviously an important consideration. If you're not specifically dealing with long-term health outcomes that are heavily dependent on therapeutic decisions, but are we using PET to make specific management changes so that patients may enter certain algorithms as opposed to others on the basis of those findings, so again, it's important to consider that in this question, if you will, the way it's phrased.

DR. SOX: Thank you. Deb, please introduce yourself.

DR. ZARIN: Dr. Deborah Zarin, the director of the technology assessment program at AHRQ, and the breast cancer report was commissioned by us for CMS. As I recall the discussion at the panel, the thing that was different about this was that there were clinical situations where the alternatives were really inadequate. In other words,

there were patients with a high prior probability or some moderate prior probability of having a recurrent lesion, or locorecurrence, and there was no other way

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to find out where it was, and sometimes PET worked, PET did identify a place where you could then go biopsy.

As opposed to one of the earlier questions somebody asked about, which is why wasn't it good enough instead of a biopsy in other situations? Those were cases where you knew what to biopsy and the biopsy didn't cause a lot of morbidity, so it was more accurate and therefore better to do biopsy. What we've heard today is clinical situations where it's not clear where to biopsy but there is a suspicion that there's something there, and for at least some patients, PET was able to sort of direct more invasive work-up. So I think that was some of the discussion. Barbara, is that your recollection?

DR. MCNEIL: I think that's correct.

DR. ZARIN: So it wasn't that they were willing to take the point estimate of sensitivity and

specificity, it was sort of however good it was, it was better than anything else that people could come up with in that clinical situation.

DR. SOX: Thanks. That's very helpful.

Barbara, let's not leave Alan's point, and I'm wondering whether we might want to discuss alternate language on this, focusing on this issue of adequate

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evidence.

DR. MCNEIL: Well, Alan had some good language. What was it, Alan?

DR. GARBER: Well, let me tell you a way it could be rephrased that I would have no trouble dealing with, and I want to emphasize, I'm only looking at the panel's internal logic. I'm not trying to make any claims that I know the evidence well or anything, but I think it's quite obvious that the panel seems to have contradicted itself by voting in the affirmative on this particular question and then also concluding the evidence is inadequate.

So my, I would say the panel seemed to

have affirmed the question, is it likely that PET improves health outcomes as an adjunct, et cetera, et cetera.

DR. SOX: Say that one more time, not quite so quickly.

DR. GARBER: Is it likely that PET improves health outcomes when used as an adjunct to standard staging tests?

I think Dr. Wahl has something.

DR. SOX: Dr. Wahl?

DR. WAHL: Again, Richard Wahl. I just wanted, before you change the text of what the

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committee voted on, I just wondered if I was clear. They did vote on the data that was presented and available to them, which was more than the published database, that this was the conclusion of the committee. So I wanted to just have clarification. Dr. McNeil said there was inadequate data on, was it your next slide?

DR. MCNEIL: The previous one.

DR. WAHL: Okay. But was that conclusion

that there was inadequate data based on your assessment as head of the Blue Cross technical assessment, or was that the committee's vote that there was inadequate assessment?

DR. MCNEIL: Rich, I thought there were two things. I thought that our judgment about inadequate data as a replacement came from the report that we were given by CMS.

DR. WAHL: I just didn't think that the committee ever voted that there was inadequate data on this particular point, that was the clarification I was trying to get.

DR. MCNEIL: I see.

DR. WAHL: Because I think that they're being put up there as equal, but I think the full committee voted on the statement but the inadequate

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data, and might be helpful, I thought was your assessment from your read. So maybe I misunderstood, but I thought it was worth clarification. Maybe you need to look at both slides.

DR. MCNEIL: Janet, could you put them back up?

DR. GARBER: Well, the other one simply says two published studies, inadequate data. It doesn't say anything about unpublished studies.

DR. WAHL: But I am simply saying that the body of evidence they examined was more than that at the committee.

DR. MCNEIL: Here was the problem. We examined critically the data that were presented to us and that had been commissioned by AHRQ and implemented by the Blue Cross TEC panel. We analyzed those data with a fine-toothed comb. We were then presented with several little summaries, 15 patients here, 10 patients there, that were largely within the rubric of we're just at wit's end. Radiation therapy has destroyed the anatomy, we really can't figure out what's going on, and there were several of those scenarios. We actually never looked at the data for those scenarios, there were no published data that anybody presented. And Rich, I have to confess, I

haven't read your article from July, so it may very well be in there.

We didn't look at any primary data and dissect the integrity of the clinical study in terms of prospective and consecutive and no verification bias and blinding and blah, blah, blah. We didn't do any of that, because all we had was somebody get up and say you know, 10 patients.

DR. BROOK: What is the health outcome that they reported to say they have influenced?

DR. MCNEIL: Treatment decisions.

DR. BROOK: So that's not an outcome. I mean in the true sense of the words, that's a process, and in terms of what they would do next to the patient. But in terms of a health status outcome or even a patient satisfaction outcome, did they present any data that was an outcome?

DR. MCNEIL: It depends, Bob, on what you mean by an outcome for a diagnostic test. If you take as an outcome of a diagnostic test that it leads you to the proper site to biopsy and therefore the

patient has only one biopsy instead of two biopsies, some people might view that as an outcome. Now they didn't present the data for that, I'm not suggesting they did, but that might be considered an outcome.

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DR. BROOK: I have no problem with the inappropriate biopsy or removal of tissue or something being an outcome, but you didn't say that they did that, because they --

DR. MCNEIL: What they said was, and they're not here, Bahs is not here, Rich is here, was to say that by seeing a lesion after one test which was indeterminate on MRI because of fibrosis or whatever, they then were able to guide the surgeons to biopsy that spot.

DR. BROOK: I'm not arguing that, I believe that's all true, I don't think there is any question about that.

DR. MCNEIL: Okay.

DR. BROOK: I think the question is, is that good or bad in terms of an outcome for the patient? Because you have such a high probability

that there is nothing there in the first place when they go through all these things, then the question of the treatment of what you do with this population is -- I mean, I have no problem that you say if you're looking for a place to biopsy in a place that has -- I mean, there's lots of reasons, there's old scarring in the upper lobe.

DR. MCNEIL: So really what you're asking

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is would they not treat the patient in whom they have a high suspicion of recurrent disease absent a pathologic marker or a histologically positive specimen, or would they treat the patient anyhow with some new chemotherapeutic agent because the prior probability of recurrent disease is so high? That's really the pivotal decision and I don't know, and we have to ask our resident oncologist, and maybe Rich knows.

DR. WAHL: Having been there, I can comment about some of the scenarios that were discussed, and I know Dr. Alavi discussed one of

them. But in the situation of brachial plexus disease recurrence, trying to tell it from radiation damage, radiation damage versus recurrent tumor, obviously the treatment for radiation damage is not chemotherapy. Some chemotherapies like Taxol which are common second line, or common therapy in breast cancer for salvage, causes nerve damage, so giving that kind of chemotherapy in somebody who already has radiation induced nerve damage would not be good. Similarly, not giving chemotherapy to somebody with cancer would be bad as well, and in some of these locations the biopsy is so difficult because the biopsy is destructive and you have the nerves that go

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to the arms, so you can end up with loss of sensory -- you know, in some locations it is just exceedingly difficult to biopsy.

And before you came in, we were discussing the fact that the MRs in these patients are often markedly abnormal with very large areas of contrast enhancement that are not specific, so in that particular situation, the decision would change a

therapy and the therapy could have adverse effects. That was just one thing discussed.

DR. BROOK: I understand that. All I'm asking is, is this, when you looked at the evidence on the panel, when they actually presented even the studies that are not published to you, did they in any way purport to show that they affected that outcome positively? I mean, this all makes a lot of logic, just like the old studies from Italy made a lot of logic for doing intensive screening in following up women with breast cancer, just like adjuvant bone marrow made a lot of logic. There are lots of things that make a lot of logic in medicine but when studied they don't -- I have no problem in saying this is a logical case that make a lot of logic, I'm just wondering was there enough even nonpublished evidence to suggest.

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DR. MCNEIL: I think that the data that were presented were of the flavor that Dr. Wahl just gave. I don't think it was anymore quantitative than

that.

DR. SOX: Dr. Conte, do you want to comment on this point?

DR. CONTE: Again, I go back to the issue I made before, that there is not much on long-term therapeutically derived health outcome data. So again, in the article that I cited in the statement this morning, 60 percent of women in this study, as reported by 32 different medical oncologists, had altered management on the basis of the PET findings. I think that that is pretty clear. They made 32 different, medical oncologists made a decision that was different in 60 percent of the cases.

DR. SOX: I would like to move us back toward whether we're going to vote on this question or another question. Alan, you had your hand up.

DR. GARBER: I think there is an important point of fact, and this fact may turn into opinion about what the panel really believed, and it's unfortunate that we don't have the whole panel here to discuss this with them, but it's whether they believe that the evidence was adequate. So we have

heard from, we have heard that the published data was clearly inadequate and I assume there was a consensus, and then you're left with unpublished data. And I guess that Dr. Wahl or Dr. Conte said that the unpublished data swayed the panel into thinking there was adequate evidence.

Now, and I think Dr. McNeil believes maybe that wasn't true, and that's what we're left with. And I think this is a crucial point, because it determines whether the affirmative answer to the question really flows from the logic that the panel engaged in. But on the point of unpublished data, I think it's important to point out that virtually every structured evaluation of evidence discounts unpublished data heavily for reasons we are all familiar with. It's pretty unusual to have, let's say it's an abstract. We've all seen time after time that published abstracts when they ultimately appear as published journal articles may have very different conclusions, including very different results. It's

very hard from many of these unpublished studies to actually know what the structure of the study was to determine whether the study design was reasonable and would lead to reasonable outcomes. And again, I'm making general points, not points about the data that

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you discussed at the panel meeting.
But this I see as an important issue, was the unpublished data enough to persuade the panel that there was adequate evidence or did it instead persuade the panel that this looked very promising, would be a useful treatment. So I think we need to reach some conclusion about that and if it's the latter, I would suggest we go with the alternative language that I proposed, or something like it.
The other point though, Dr. Wahl has talked about circumscribed settings in which this could be very useful, which I think is important for us to know and important for CMS to know in determining a reimbursement policy, but he's describing situations that are much more narrowly circumscribed than the ones in the language on this

question. So that's something I think CMS needs to deal with. It's suggesting that there are some conditions in which the added information from PET could be extremely useful, but that may be a small subset of conditions that fit under this language.

DR. SOX: Well, I put on the agenda for this afternoon's discussion something to the effect of unpublished and late studies and how panels should deal with those, which I think the Executive

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Committee ought to discuss that and try to give some direction to the panels, but meanwhile, we need to move this discussion toward a vote. Alan, you directed a question to Barbara. Barbara, do you want to respond?

DR. MCNEIL: Alan, I think this is a very troubling question. I presented the deliberations of the committee, but I cannot emphasize how much we struggled with this, and I don't think anybody would want to die on the basis of the decision that they made, so I think we made a considered judgment

listening to the facts, but the judgment was not as rigorously based as it was for the other questions. That is just a fact. We did the best we could, but I can honestly not say it was done with as strong an information base as we had for the other questions. So, having said that, the answer to your question, which was did we view it on the basis of adequate data, did we make a judgment on the basis of adequate data or did we make a judgment on the basis of promising or likely, it was clearly not the former, clearly not the former, because we just had, you know, I saw 11 patients kinds of scenarios, so we did not look at anything rigorously presented. So we can definitely not say it was based on adequate

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evidence, and you're right, the wording here is all wrong.

DR. SOX: So we really need to change this wording?

DR. MCNEIL: The wording has to be changed and I'm sorry we didn't pick that up ourselves.

DR. SOX: So is it likely that rather than

is there adequate evidence, it is likely that?
DR. MCNEIL: It is likely that is closer to the spirit of the group. Alan also, however, raised the issue about whether our discussion relayed to the whole panoply of patients with breast cancer or with a more narrow subset, I think is what you were asking, and as I recall, it was a more narrow subset. Sean was there, so you could probably recall this as well, or Deborah, we really were concentrating largely on the specific areas in the head, neck and axilla, but we didn't have any information on the other areas, to my knowledge.
DR. SOX: So you accept as a friendly amendment from Alan the substitution of --
DR. MCNEIL: It is likely that.
DR. SOX: Is it likely that, in the form of a question.
DR. MCNEIL: Yes.

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DR. SOX: Okay. So that's been resolved. Now we'll go on to other people. I don't know who

had their hand up first. Bob will start.

DR. BROOK: I'm just wondering if we just ought to state what the person stated, that there is adequate evidence that PET improves, changes decision making.

DR. MCNEIL: I don't know that we had data on it. We did not review that article, Bob, so I can't say that that was a good article.

DR. BROOK: Well, you had a lot of unpublished data and you had reports that people changed decision making. And you also have evidence that they changed decision making based on a logic that would relate, an implicit logic, a medical clinical logic that would relate that to outcomes, but there is no evidence that that logic has been tested to affirm that that is indeed true. That seems like what you're saying.

DR. MCNEIL: No, that's not what I'm saying. I do not believe that we had at the time, and I cannot accept information from an article that the panel has not yet reviewed, that those studies were adequate to show that patient management was

changed. It is likely that, I accept that, I cannot

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accept the adequate in patient management.

DR. BROOK: Well, we're not making the coverage decision. If HCFA wanted to say, or we wanted to say from your panel, was there enough data presented in some form, that the panel believed there was adequate data to show the tests were being used in a way that changed from a prior to a post decision of what could be done, because that's important for HCFA to put in the hopper if it decides to make, or when it decides what to do with the coverage decision.

That sounded like you were all in agreement, and indeed you believe that there was enough data in the series available to support that doctors were using these data to change their decisions.

DR. MCNEIL: Well, again, it depends upon what you mean by data, Bob. We did not have an adequate review, we did not critically review the

data to suggest that I would feel comfortable speaking on behalf of the committee to say that the data were adequate to support that PET improves management decisions. It may be true but we did not have the data at our hands to do that, and I don't know about this one article in September's JNM. I do

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believe we supported the decision that it is likely that.

DR. SOX: Okay. Staying with this point, Wade.

DR. AUBRY: Yes. Before we change the question, I would like to just add another dimension and that is the issue of prognosis or prognostic information. Much of the discussion we have had about unpublished evidence or data is basically that it would change management decisions, but another piece to this is prognosis, and if PET shows that it's Stage IV disease rather than local disease, then that's obviously a significant prognostic issue, and I wondered if that came up in the discussion or was that mentioned, because some people feel, myself

included, that prognostic information is a health outcome.

DR. MCNEIL: We discussed the questions that were asked of us and reviewed the data associated with those questions. If you were to ask about whether PET, I guess the question you're asking me is should PET be used at the time of the initial diagnosis of breast cancer to stage patients; is that what you're asking?

DR. AUBRY: That's not what I'm talking

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about. This specific situation we're talking about, the adjunct situation, where the unpublished discussion seems to indicate that there are some patients who were thought to have local disease who were in fact found to have distant metastases or Stage IV disease on the basis of this adjunctive test after others were done and not shown that.

DR. MCNEIL: That's correct, so really implicit in the wording here is, whatever wording we take, if we detected distant disease then we've

obviously changed stage, just by definition and then that obviously changes prognosis, so they are implicitly part of one another, right? So I don't know that we need a separate question about prognosis because that's imbedded in the whole discovery of distant disease.

DR. AUBRY: Yeah, maybe there's not really an answer to that question. I think it is something to keep in mind because we seem to be struggling with the idea of this unpublished data changes management, it's unclear whether that improves health outcomes, it may well improve health outcomes, but we don't know, but prognostic information itself may be very important to a patient, maybe an outcome a patient could feel regardless of whether that change in

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treatment management actually improves the health outcome of the patient in terms of survival. I just thought we should factor that into the discussion as well.

DR. SOX: Dr. Conte, did you want to make a comment at this point?

DR. CONTE: Yes. I just want to point out that the panel felt on the basis of what was presented and what was in the literature, both, that there was adequate evidence to answer this question. That's what they voted on. This was what was presented to them.

I think it should also be disclosed that five voted affirmatively and one abstained. The person that abstained, if I'm not mistaken, was Dr. McNeil.

DR. MCNEIL: No, that's not true.

MR. CONTE: That's not correct?

DR. MCNEIL: No, it's not.

DR. CONTE: You voted for? Who abstained?

DR. MCNEIL: I don't know who abstained.

MS. ANDERSON: I think it was Jeff Lerner.

DR. CONTE: Okay. So the fact of the matter is that the majority of the members of the committee voted this question that there was adequate

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evidence presented at the Diagnostic Imaging Panel

for this indication.

DR. MCNEIL: You know, Peter, I'm not sure about that to be perfectly honest. We would have to go back and do a line-by-line analysis of the minutes.

DR. CONTE: I have the minutes here.

DR. MCNEIL: Okay. If we voted that, just to be -- if you want the spirit of the deliberations, and I don't know whether you do, Dr. Sox.

DR. SOX: Well, it's our job to try to capture the spirit of the discussion, and we as an executive committee can alter the wording of a resolution if we feel by so doing it fits, it more adequately describes the tenor of the discussion, and we listen to you as the representative of the panel to give us advice on that.

DR. GARBER: How they voted, that's a matter of record.

DR. MCNEIL: The sense of the panel, whatever the word of the deliberations was, and I tried to convey it in my remarks by saying had the wind blown a little bit differently, the five to one

vote could have switched. I mean, that was realistically the way we were thinking about it, so I

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do not believe that the spirit of the committee was that there was adequate evidence. I think Alan's assessment of the wording is much closer to what our feelings were at the time.

DR. SOX: And I personally believe that the committee ought to be listening to Barbara rather than the record as it's reflected there, and trusting Barbara as a representative of the panel to tell us.

DR. BROOK: I really don't understand, I must object. Barbara voted for this thing, Barbara understood the words of this thing, this is what was voted on.

DR. MCNEIL: Well, could I just clarify, Bob?

DR. BROOK: I really don't understand what we're doing here.

DR. MCNEIL: Let me clarify for you. What happened, I prepared these slides quickly at three

p.m. yesterday when Janet told me I was making the presentation, so prepared these slides 15 minutes before leaving for the airport. So if there is some sloppiness in the wording, I apologize. If I had had more time --

DR. BROOK: So this is not what you voted on then? Can we get the minutes from the committee

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of what actually -- I mean do we know, because what we're being asked to do is overturn a vote that the chairman of the committee voted for and is now presenting it differently here. It's not like there was vast disagreement and we're being asked to, this was so close. A five to one vote doesn't look very close. You as the chairman voted for it, and is this what you all voted for?

DR. MCNEIL: I do not believe, Bob, that this is what we voted for in spirit. I believe what we voted for was Alan's wording.

DR. TUNIS: Can I make a comment, because as another person who was at the meeting and, I believe, it seems to me a fair amount of this

confusion is simply over different interpretations of what the word evidence means here. I think what the committee concluded was that the published evidence was by itself inadequate to support a conclusion of the clinical benefit, health improvement of using PET under these circumstances.

The committee listened to a lot of public testimony and there was a lot of discussion about the logic of using PET in various specified circumstances. Dr. Wahl described some of them, others described some of them, and I believe when the

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committee voted on this question, they were including using evidence as a broad term to mean not just published and unpublished evidence but the expert testimony that was provided. And so all adequate evidence meant here was the body of everything we have heard supported this conclusion, just barely, but the committee was willing to support that five to one.

If they had specifically asked the

question, is there adequate evidence from these two published studies to support this conclusion, I believe the committee would say no to that question. They're just two different questions that seem to be wrapped into the same question. So I don't really think there is as much disagreement here as it sounds like.

DR. MCNEIL: So we should have had a second mitosis on this question.

(Laughter.)

DR. SOX: Anybody else want to pick up the discussion at this point?

DR. FRANCIS: I think I understood what was just said but I want to be clear about this, because I thought really that two different problems for the committee keep getting put together. And one

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of the problems was what to do with either unpublished or new studies that happen after you get a TEC report, okay, so that was one problem, and how do you decide whether they are adequate or not or how do you think about them.

The other problem was what to do when the question changes, so that the question that you ended up talking about was, does PET affect patient management in the very narrow class of cases in which you tried other diagnostic modalities, there is a high suspicion, high prior probability of recurrence, and the other diagnostic modalities haven't told you anything informative. Does PET in those circumstances affect patient management, which is a different question than -- the original question that the panel was asked was a much broader question. So two things were going on. One was new studies were getting thrown at you, and the other was that the question was being changed. And so what you ended up saying was that there is a logic here, but there isn't any evidence. I think that's what Alan was saying a while ago. I don't know whether one would want here is changes in patient management, changes in prognosis or changes in outcome, but it's clear there are changes, and at least clinicians do

change management because they can find the place to biopsy in that very very limited class of circumstances.

DR. SOX: Could I just read from the minutes a selection that is I think pertinent to our discussion. It states here, and this is in respect to this indication, at the request of the HCFA medical officer Mitchell Burken, M.D., the panel discussed the level of effectiveness of PET in this indication, what we're talking about, but was unable to reach consensus upon which level of effectiveness had been established by the evidence.

So it does sound like you did not come to a conclusion about whether the evidence was adequate or not. I think this statement from the minutes supports your interpretation of the sense of the meeting at that time.

DR. MCNEIL: I think that is absolutely right, Hal. I think what Leslie has said though, and is probably the reason, and what Sean said earlier, why we're having this discussion now is the fact that the committee felt, was really very very confused in

having data presented to us without having the ability to digest it clearly and carefully, was something that we really had not expected and did not

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know how to deal with in an effective fashion, so we had really two options, as I recall.

One was, because I don't know that the guidelines for this have been entirely worked out yet for this panel, but dealing with new data, when somebody gets up and says 11 patients and two of them were this and three of them were that, and they were followed for three months and the MR was this, it's very very difficult to do. So we were left with two alternatives. One was to basically table this and say bring back the data that everybody has presented in a structured format and have us review them, take all the published data that Rich says is in his article, and review it and then make a judgment. Or vote on it with some less rigorous approach to our interpretation and to modify, despite what the wording says or what the minutes says, we did not

believe the published data were adequate. So to have some kind of sentence there that reflected that it is likely that on the basis of the anecdotal information that was presented to us, that this would work. But on behalf of our committee, I would like very much to know what to do with new data, new questions that come up on the spot, because I don't think we can deal with them properly.

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DR. SOX: We will discuss that this afternoon. I think we ought to take a vote as a way to resolve this issue, and we'll just give Dr. Zarin a chance to speak, and then I would like a motion and a vote.

DR. ZARIN: I would just like to make two points. One is, I think that, I guess it's now called Alan's proposed language, did capture the spirit as I heard it, with one proposed addition, which would be I forget the exact language, but is it likely that the use of PET as an adjunct will help, I think putting in the words some patients, which isn't as precise as many people would want, but I think

that the panel as I recall it was talking about a more narrow group of patients than that would imply, but wasn't really able to specify exactly what that group. You know, the spirit was there were some patients for whom there is nothing else that's going to be helpful and this has been reportedly helpful sometimes. So think about something like the word some.

The other thing I'd caution you against is saying that you're doing this because you're accepting change in management as the outcome. I think in the negative answers to some of the earlier

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questions, Barbara pointed out that the reason for the negative answer in part didn't have to do with the fact that they didn't think PET would change management but that they were worried that the change in management would be based on misinformation, so that there was a worry about undertreatment, either under biopsy or under dissection of the nodes because of false positives or false negatives.

So that, I think the panel in other instances with PET was worried that the change in management which would occur would not be in the patient's best interests. However in this instance, there was more a sense of knowing where to biopsy, somehow I think must have felt more secure to panel members than knowing not to biopsy or not to dissect lymph nodes.

DR. SOX: So at this point we're going to entertain, give somebody an opportunity if they wish to make a motion about changing the wording of this recommendation so it fits a little bit better with the published record and the account given by a number of observers of that discussion. And then we will go on to discuss the rest of the report and actually make a vote for approval or disapproval, and further discussion will occur in the context of

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discussing the motion.

MS. ANDERSON: Before we do that I would like to make a statement for the record. For today's panel meeting, voting members present are Wade Aubry,

Robert Brook, Barbara McNeil, Thomas Holohan, Leslie Francis, John Ferguson, Robert Murray, Alan Garber, Michael Maves, Joe Johnson and Daisy Alford-Smith. Dr. Harold Sox will vote in the event of a tie. A quorum is present, no one has been recused because of conflicts of interest, and now we can go ahead with the motion.

MS. RICHNER: May I say one thing before you go forward with a motion?

DR. SOX: Yes.

MS. RICHNER: I would like to know the generalizability of this data to the Medicare population of 65 and older, so what, does anybody have any idea what the scope of this population would be for this decision? I mean, what are the numbers of patients that we're talking about here that would actually benefit from this coverage decision?

DR. SOX: Well, breast cancer is a very common problem.

MS. RICHNER: I know, but 65 and older.

SPEAKER: About 150,000.

MS. RICHNER: About 150,000, okay.

DR. SOX: Bob?

DR. BROOK: You know, I don't know if we have to do anything, because when I read the complete minutes under number 4, which you read a piece of it, the sense of what the committee did is absolutely reflected in there. They said the evidence was adequate but they couldn't judge the effectiveness, they contradicted themselves. And I wonder whether we can improve what they did. That's what they did, and we could just add a note saying that because they couldn't deal with effectiveness from the MCAC committee approach, from our committee approach, this means that the evidence was inadequate based on the guidance that we had given the committees in the stuff we have done before. Because if the evidence was adequate, they ought to have been able to answer the last question.

So instead of overruling what they did, why don't we just accept what they did and make a very simple statement that says we're disturbed by

the contradiction between the first task and the second task under 4, because if the evidence was really adequate, then they ought to have been able to reach a consensus on the level of effectiveness,

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which they were unable to do. Without changing wording, without trying to second guess and change all this other kind of stuff, which undermines the whole process of the panels, why don't we just accept -- I would propose we accept this, and we point out to HCFA the fact that because they couldn't do the last part as opposed to the front, that this does not fulfill in some way the guidelines of adequate evidence as decided by the MCAC in its instructions in terms of what adequate evidence means.

DR. GARBER: Are you saying to ratify this, Bob?

DR. BROOK: They did it. I don't think it's fair. We have to go back to the whole panel process. I mean, every time we open this there is a can of worms, because on all the other motions they

said, well, changes in medical treatment may not be adequate to do this, all of a sudden we have somebody get up and say well, this may change where to biopsy or whether you want to have more radiation or chemotherapy. I believe all that and for any one of those other statements, you could have said exactly the same thing. Somehow on this one, they concluded this. They concluded it in a very wishy-washy way. And all we need to do is point out as we

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ratify this report to whatever this place is called now, that the bottom line is the panel itself contradicted itself in terms of this question and point out to the panel without trying to do anything further, and it's in the minutes.

DR. SOX: I want to get this discussion over with and the best way to do that is to have a formal motion, a discussion of the motion, and then the committee can decide whether or not the proposed language is the language they want to vote on, and when we vote ultimately to affirm or disaffirm the panel's work.

So if you want to do this, Bob, make a motion.

DR. BROOK: I move to adopt the language under section 4 as the sense of the panel, and not just the first part. There's two pieces of it. You read the second part.

I move we accept the full discussion under 4. There are two parts to it, that they said yes to the question and no to the level of being able to identify the level of effectiveness.

DR. MCNEIL: We actually separated -- I don't know what you're reading from, Bob.

DR. BROOK: Your minutes. Now if these

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minutes aren't accurate, then there is something really -- I mean, this is, whoever Janet Anderson is.

MS. ANDERSON: That would be me.

DR. BROOK: Hi, Janet. You certified the minutes.

DR. MCNEIL: So what we actually voted on, Bob, was we actually split question 4 formally when

we voted.
DR. BROOK: Which is right there, but there's a second part to it.
DR. MCNEIL: No, there's a first -- you came in late. There is a previous slide that shows we actually split question 4 when we voted.
(Inaudible colloquy, several people speaking.)
DR. MCNEIL: This is how it was presented, if you look up here, this is the original question. The operative phrase is in blue.
DR. BROOK: You resplit it.
DR. MCNEIL: We split it into two parts.
DR. BROOK: Okay. I'm looking at the minutes.
DR. MCNEIL: Okay. I'm telling you what we did.
DR. BROOK: Okay. Did you take a negative

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vote on that?
DR. MCNEIL: Yes, we did.
DR. BROOK: Where?

DR. MCNEIL: We took a negative vote on the replacement and an affirmative vote on the adjunct.

DR. BROOK: It says the question was then changed, but did you deal with the other piece of the question?

DR. MCNEIL: Yeah. Look as it is now, Bob. The question was split into two parts. This is the first part --

DR. BROOK: You say there's negative --

DR. SOX: Don't interrupt, okay. Let's not interrupt each other trying to get through this discussion.

DR. BROOK: Okay. So that becomes question 5, so that was the original question?

DR. MCNEIL: Forget about the numbers. We voted on this question, and then we voted on the next question.

DR. BROOK: No, you voted on that question and then you were requested by, I'm following the minutes, you were requested by the HCFA medical

officer to indicate the level of evidence for this

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question, and you couldn't reach agreement.

DR. MCNEIL: We could not. No, it wasn't that we couldn't reach agreement, we just didn't know what it was. There was no discussion about whether it was big or little.

DR. BROOK: This says that you were asked to -- I'm just trying to read -- discuss the level of effectiveness but were unable to reach a consensus on what level of effectiveness had been established.

DR. MCNEIL: And if I could state precisely what happened, that is we did not know. I didn't say it was a big one and somebody else said it was a little one, we just didn't know.

MS. ANDERSON: As the author of the summary, I can state for you that this is an abbreviated version of the minutes and as a summary of the minutes, this is capturing -- there were four abstentions when we decided to vote on the level of effectiveness so it didn't carry, it wasn't a motion that didn't carry.

DR. BROOK: Hal, is there some way because this contradicts the first part of this, that we can just say that, and vote on it? I mean, if they can't define the level of evidence and they said the evidence is adequate, what's the policy here?

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DR. MCNEIL: I will take full responsibility here for making a mistake. If we want to talk about the exact word-by-word description of what is in those documents, that's one line of thinking. If we want to talk about what the spirit of the discussion was as well as I can synthesize it, I'm happy to do that. I can't mix both of them up in the same paragraph, so which would you like me to do, Dr. Sox, the word by word or the spirit?

DR. SOX: Personally, I think we have had a number of attestations to the spirit of that discussion and they are all in the same direction and I think that's the route we should go.

DR. MCNEIL: So if that's the route we want to go, I take full responsibility in making an

error on this slide as I was rushing to the airport with 15 minutes to go in my wording for this question.

DR. SOX: Okay. Now, with that, I would like to entertain a motion to change the wording. If there is no motion, then we will vote on what we have. Would anybody like to make a motion that will clarify the discussion so that what we're going to vote on comes closer to what has been described as the character of the discussion? Alan.

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DR. GARBER: I would like to move that we modify the language as I previously suggested, is it likely that PET improves health outcomes when used as an adjunct, keeping the rest of the language. I don't know whether this would be part of the same motion or not, but I think there should be instructions to HCFA staff that it was the sense of the Executive Committee that the specific uses for PET in this setting need to be more clearly delineated, and also to reflect the spirit of the panel, and that could be separate.

SPEAKER: For some patients, did you want that?
DR. GARBER: Yeah, for some patients.
DR. FRANCIS: Shouldn't your motion be that we affirm the decision of the panel insofar as what you just said, and otherwise not -- we don't change what the panel did.
DR. SOX: See, we're trying to get some language so that we can make a vote either indication by indication or for everything, and so that is a second step. So Alan, please repeat your language and we will see if there's a second, then we will have a discussion of your language and hopefully vote.

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DR. GARBER: The first line becomes, is it likely that PET. Second line is modified so that it says, improves health outcomes when used as an adjunct to -- yeah, for some patients. When used as an adjunct to standard staging tests in detecting, et cetera, et cetera, and when it says when results,

for some patients comes before when, so it becomes for some patients when results from other tests are inconclusive.

DR. AUBRY: Can you read it now so what it says, is it likely there is adequate evidence or is there --

DR. BARBER: No, no. Adequate evidence is struck. Is it likely that PET improves health outcomes --

DR. MCNEIL: Janet, could you change that on line now, can't you just edit it?

MS. ANDERSON: Yeah. If someone wants to second, I can read the full motion.

DR. MCNEIL: I second.

(Inaudible colloquy.)

MS. ANDERSON: Okay. The motion is to change the wording of question 4 to, is it likely that PET improves health outcomes when used as an adjunct to standard staging tests in detecting

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locoregional recurrence or distant metastases recurrence for some patients when results from other

tests are inconclusive.

DR. SOX: Now that language is open for discussion. Bob?

DR. BROOK: Barbara, if I went to question 1, 2 and 3 in your minutes and substituted that language for adequate evidence for each one of those questions, which says it may affect some patients and there is a likelihood, would you have voted yes on all of those motions?

DR. MCNEIL: We would have voted no on none of the motions except for -- we would not have voted yes on any of the motions.

DR. BROOK: Is there some likelihood, is there likelihood that PET can improve health outcomes by leading to earlier diagnosis or breast cancer compared to short interval mammography for some patients? If I change that the way I have changed it now under 4, my guess is it would be almost impossible for the panel not to have voted affirmative on those questions because all that means is somebody has to come up and show that for three

patients it made a difference. That's all that has to happen.

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This trivializes the question that you were asked to do. You were asked to look at adequate evidence to find out whether there's adequate evidence against some method. The way we have rephrased this question is a noninteresting question.

DR. MCNEIL: Well, I don't know, Bob, if you had a chance to read the report, did you?

DR. BROOK: I did not read the whole report.

DR. MCNEIL: If you read the report, you would see that if you just look at the data and the clinical logic, it would be very difficult under any circumstances, and I can ask Sean or some of the others who are here to say that our vote would be changed under any scenario of additional information. The implications of false negatives on undertreatment in a majority of the situations was just enormous, and I don't think there is any circumstance that would have change.

DR. SOX: I read the evidence report and I concur with Barbara's judgment. Mike, you're next.

DR. MAVES: The problem I have is I understand where we're going and I understand what we're trying to do in the spirit of the discussion. The difficulty I have is I think from a procedural

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standpoint. I do sort of object to changing a question and then ascribing the votes that took place in a meeting a period of time ago to that changed question. I would, I think we were getting close there, I would accept the report, accept the votes, but then obviously annotate this question to state that after discussion at the Executive Committee we felt that the spirit of the discussion more closely answered the question, and then put Alan's question, because I do think it does capture the spirit. But I have to say, I'm bothered a little bit by changing language in a question and then ascribing the votes of the committee who aren't here to sort of challenges or to revote, and I think Bob

has a lot of merit in what he says. If we had changed other language on other questions, that could have changed as well. But I think it's a way of, what you want is the spirit of this to help guide HCFA in the decision making process, but I think we really can either accept or refute the report and the questions that were asked. I'm bothered by changing the question and then ascribing the vote to that changed question.

DR. SOX: Well in that case, you should vote against the motion, and then we can consider

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another motion. Alan?

DR. GARBER: Actually, I completely agree with both Bob and Mike, that we don't want to change the vote of the panel members, and I hope nobody took my motion in that spirit. My motion is really about what we the Executive Committee conclude, not about what the panel concluded. What the panel concluded is a matter of record, we are not trying to rewrite the history, but there is an obvious glaring contradiction in the panel's deliberations if we take

as a given that in fact they did not believe that the evidence was conclusive.

So rather than us ratifying the panel's conclusion or in any way saying that we thought it was correct, we are trying to capture the spirit of what we believe the panel intended by substituting some language and adopting something closely related to their conclusions as the Executive Committee. So my motion is about what the Executive Committee concludes, not about what the panel concluded.

DR. SOX: In any case, this is advice to HCFA about the state of evidence, so it's not like we're making a judgment that is absolute, it's simply giving advice to HCFA.

DR. MAVES: Hal, if I could ask Alan then,

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I assume that my comments then are not different than what you intended by your motion?

DR. GARBER: No, I think we intend the same thing.

DR. MAVES: Would you accept that then as

a friendly amendment, I suppose is the next question.
DR. GARBER: But if we do not ratify the panel -- this is the Executive Committee's conclusions which we believe reflect more closely the logic of the panel's conclusions, but this means we don't necessarily accept the panel, I mean we accept it as a fact that that's how they voted, but we don't in any sense endorse it.
DR. MAVES: And I think that's consistent with where I'm coming from.
DR. SOX: Would anybody else like to discuss the amendment as it now is projected on the screen? Daisy?
DR. ALFORD-SMITH: It's really not an amendment, it's really a comment by the Executive Committee, because if it's an amendment, you're replacing what the panel said.
DR. GARBER: Yeah. This is amended language. In other words, this is the Executive Committee's own recommendation and it uses amended

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language, so yes, what Daisy says is quite right.

Again, we're not trying to say they didn't vote as they did and we're not trying to say they voted on something different than they did. We obviously can't do that and we wouldn't want to do that. This is amended language which we are adopting as the Executive Committee's recommendation.

DR. SOX: As our recommendation to HCFA.

Wade.

DR. AUBRY: As a new member of the Executive Committee, it seems to me that we were asked either to ratify or not ratify this decision, and what is the sense of the discussion in the last few minutes is that several members of the panel here are not comfortable ratifying the exact language, the original language. And therefore, I would say that perhaps we should not ratify this and then have a substitute motion which Alan has made, which is the sense if it's voted affirmatively, would give the sense of the Executive Committee on what transpired at the meeting of the imaging panel.

So, I guess my question for HCFA staff or

for Dr. Sox is, are we being asked as an executive committee to ratify or not ratify, is that what we are being asked?

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DR. SOX: I think we're being asked to approve or disapprove the language of the panel and if we disapprove it, we can either do that in a way that qualifies our disapproval, which might be to approve another statement that we think more accurately reflects the discussion and the evidence. So, Alan?

DR. GARBER: Well, maybe, can I accept Wade's comment as basically a friendly amendment? What my motion was intended to do was in one step deal with what Wade is talking about doing in two steps, that is, the Executive Committee does not approve, ratify, whatever the operative language is, the original recommendation of this particular item 4.B, I guess it is, of the panel, and accepts all the others. But it does approve a closely related amended version of that as the Executive Committee's recommendation, which is the language that I

describe.

DR. SOX: So, if I understand Wade correctly, I think you were stating that what we really should do is to express our dissatisfaction with the statement as approved by the panel and as reflected accurately in the minutes, and then if we don't approve that language, if we think it is

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basically an inaccurate statement of the state of the evidence, then approve substitute language.

DR. AUBRY: That's correct. It's a first order, second order issue.

DR. SOX: In that case, I think we'd have to, if we wanted to move in that direction, then the original proposer, I think -- I'm getting a little bit beyond Roberts Rules of Orders, or my understanding, but I think you could withdraw your motion.

DR. GARBER: Well, consider me having withdrawn it and substituted, and actually I think it's a friendly amendment, which then the seconder,

who was Leslie, would have to approve.
DR. FRANCIS: I agree to that.
DR. SOX: So am I correct then that you have withdrawn your motion at this point?
DR. GARBER: No, I clarified it. I'm accepting a substitution in the motion as it was just stated.
DR. FRANCIS: And I second that substitution, which is that we accept all but the one that has been the subject of discussion, and we also accept the closely related as our recommendation to HCFA.

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DR. SOX: I'm sorry. I'm now the one who's having trouble here.
DR. GARBER: The motion as amended, and as seconded, is that the Executive Committee approves or ratifies all of the recommendations of the panel except this one, which I believe is 4.B, and the Executive Committee makes an alternative recommendation which is the following, and that uses our language.

DR. SOX: So that's really a compound motion?

DR. GARBER: Yeah.

DR. SOX: Are people comfortable with doing it that way, or would you prefer to vote first to approve the original statement and then if we decide to not to approve that, then we could approve a modified statement that would change the language of 4.B and we could vote on that.

DR. MURRAY: I'm comfortable with Alan's motion.

DR. MAVES: I am too.

DR. SOX: It sounds like we have a majority of the voting members who are comfortable with handling it in the manner Alan has proposed instead of as a single motion. Yes please?

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DR. BROOK: I'm sorry to do this but I think what we've been trying to do is set up a process to increase faith in the panels. You have an easy way out here. All you have to do is say the

Executive Committee has read the discussion in the minutes under 4. Because the panel themselves were unable to reach a consensus on the level of evidence, they said that, they couldn't reach a consensus, that procedurally we cannot accept motion 4 that the panel found, that there was adequate evidence. They themselves contradicted themselves, and we ought to just vote that we can't do that.

We ought not vote on the new motion. We could encourage HCFA. We haven't seen the evidence. We're now subverting the whole damned process that somebody spent two days sitting there, voting a new motion without looking at any evidence and without having been tasked to do that. Our job would then be to say if we think there are other unresolved issues about this procedure, it ought to go back to the diagnostic committee with a note from us to say would you please consider these kinds of other questions, because we think they're important.

We can't be a second judge here, because it's going to stop anyway in January, and why don't

we set the precedent here to actually look at the process which is what we have been trying over the last year and a half to do. And you've got an out here. It's absolutely clear that you can just say we can't accept this motion because the panel themselves didn't.

DR. MCNEIL: Hal, I think this goes back to what I talked about earlier and I think we should be voting, I think I'm being an impartial observer of the process, and Sean is here and several others were here as well. I think that what is there, Bob, is what we in spirit were voting on.

DR. BROOK: This is a legal process. We spent hours and days going through public comment and all of this about the process. We word smithed these documents that we gave to the panels umpteen times. We're trying to improve the panel process. If we sit here and in two hours come up with a new question and a new vote because we think we did this better than you did it, we're subverting this whole process. Even though we may be correct, I will give

the notion that Alan and Hal are correct on this, this is what it would come out, that's not the issue. The issue here is, we've got to build up a strong process where when people come to testify in front of

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these panels, they have confidence that the panels are going to come up with decisions, that we are going to look at their decision, and as long as the process is fulfilled in the way that we've talked about it, that we would then go ahead and improve the process and not second guess everything. Because then we ought to have another open discussion, we ought to hear those cases, we ought to spend as much time as you did on it. You guys spent much much more time on this and read many more articles than we have. And I'm just urging us to be faithful to the process.

DR. TUNIS: Let me just as a point of view of process and what would be helpful to us, because I think, you know, all the ideas are on the table and I don't think you can give any clearer sense to HCFA, CMS than you have already. So I think, I don't think

it's worth actually going round and round on this. I think to kind of go along with Bob's suggestion, I think what would be helpful to us you go ahead, and if I'm getting you right, Bob, essentially you don't ratify this recommendation because it's internally consistent, so it's not ratified. You ratify all the others if that's what you want to do, and we've got the spirit of your new question, so we understand

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what you think the panel really meant, and you don't need to have a motion or need to vote on a motion related to that. We've got the point.

So in terms of following the process, I kind of agree with Bob. If everything I have heard, if I understand everything I've heard, the motion should be not to ratify number 4.B, ratify everything else and leave it at that.

DR. SOX: A comment on Bob's suggestion and Sean's comment?

DR. GARBER: Well, I think Bob's suggestion has a lot of merit and strictly speaking,

that might be what we should do procedurally. And the reason that my proposal is different is simply that I don't believe this is a case where we are really second guessing the panel. I think that there is an internal contradiction in what the panel did, that it's revealed in the minutes and in the transcript. We are not trying to relook at the data or anything of the sort. It's just that the panel had difficulty reaching a conclusion and they ended up voting on a motion that seems, they ended up voting in a direction that seems contradicted by the discussion.

And we could either throw it back to them,

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but this, my motion and the amended language was intended to preserve what we thought was the spirit of their discussion, and I don't think this requires going back to the committee if what Barbara says is true, and I would tend to believe her, that the panel would have been quite comfortable with this substituted language. I think that this process has to move things forward in a timely fashion, we have

heard that over and over again, and to simply say throw this out because they didn't follow procedures, I think would not be that helpful at this point, even though I have the same reservations that Bob has about the failure to follow the guidelines that the Executive Committee recommended.

So I don't really see this as a slap in their face as much as a way to try to refine the recommendation that resulted from their discussions. And of course I think we should do what's helpful to HCFA, or to CMS, excuse me, but I still stand by this amended form, which I think moves the process forward and more clearly reflects the intent of the panel.

DR. SOX: I would just like to point out that this committee in the past hasn't been shy at all about disapproving recommendations of panels and sending them back for reconsideration, so we have

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done that, and we'll do it again if we're given a chance.

Now, we have a motion before the group and

rather than talk and talk and talk, I would like any discussion to be directed at Alan's motion, which I think we need to repeat just to get us back on target, and we need to discuss that, we don't need to start new things until we express our opinion as a group about whether that captures our views on the subject that we have just been discussing. So, could you reread the motion?

MS. ANDERSON: Here's what I have. The motion is to approve all recommendations of the Diagnostic Imaging Panel except number 4, and amend the question number 4 to state, is it likely that PET improves health outcomes when used as an adjunct to standard staging tests in detecting locoregional recurrence or distant metastases recurrence for some patients when results from other tests are inconclusive.

DR. SOX: That's the motion. We're going to talk about that motion. We're not going to introduce any new ideas until we express our opinion about this motion. So now, discussion on the motion. Mike.

DR. MAVES: I have some concerns about this, only because Bob made one other comment. He said this is a legal process and as we're finding out, words do matter. I guess maybe a question to Sean would be, does a change in language from is there advocate evidence to is it likely, would that perhaps dictate a change in how HCFA or CMS would consider covering this particular clinical situation. It would seem to me that's a weakening of position and so again, the words could matter and you might want to have the committee look at this again.

DR. TUNIS: You know, my honest answer to that is no, it wouldn't change how HCFA, you could change the words and it wouldn't change where we would be obligated to or inclined to go. Again, I would just say on that point, what CMS pays great attention to is not just these recommendations on the vote, but the logic and the discussion that go around them, and I think I would say that we have a pretty clear sense of where this discussion is going and

changing the words or however these motions come out isn't going to affect that.

DR. SOX: Thank you, Sean. Yes, Bob?

DR. MURRAY: I believe the question has been adequately discussed, and request that the

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chairman call the question.

DR. SOX: Call the question.

MS. ANDERSON: All voting for the motion? All voting against? No abstentions.

DR. HOLOHAN: Yes, I abstain.

MS. ANDERSON: Oh, one abstention. The vote carries.

DR. SOX: So, we have just approved the recommendations of the panel with the exception of 4.B, where we approved the substituted language indicated here. I think that we're done.

DR. MCNEIL: It would be nice. I'm sure that the committee wasn't anxious to come back to this question and discuss it once more.

DR. SOX: Bob, did you have a question?

DR. MURRAY: I have a question, if I

could. This is a question to Barbara and it does not change the vote, doesn't change anything, it is just something to put in the record for clarification. And if you cannot answer the question in 25 words or less then I withdraw the question. The last clause is, when results from other tests are inconclusive and I focus on the word inconclusive. Did the panel think of inconclusive as meaning an inadequate study that is for technical

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reasons, the MRI could not be done, the scan whatever was just technically inadequate, or was the panel thinking of inconclusive meaning the study, the bone scan was technically perfect, it gave a clear result, but it does not give the oncologist 100 percent certainty on the diagnosis, and therefore I want to add one more test, one more bit of evidence. So was it, does inconclusive mean technically inadequate or interpretationally insufficient?

DR. MCNEIL: It was not the former, it was the latter, and the example that Rich Wahl gave about

an MRI in which it was impossible to differentiate radiation fibrosis from new disease or recurring disease is the best example I can think of. The study was perfect, the findings because of previous therapy just didn't allow the interpreter to make an exact diagnosis.

DR. MURRAY: Thank you.

DR. TUNIS: Barbara, I have one more question for you with the same 25 words or less caveat.

DR. MCNEIL: Boy, this is tough.

DR. TUNIS: It seems to me that on this series of questions that the panel addressed, in a couple of cases, for example on the use in staging

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the axillary lymph nodes, it seems to me that my sense of the panel's conclusion was that the evidence was adequate to determine that PET was not useful, whereas in number 5 in terms of use in monitoring response to therapy, the conclusion was there is inadequate evidence to make a determination about whether it is or isn't useful.

It's a critical point for us because as you know, the structure of the coverage decision at least as of last December, you know, a voice that CMS would be inclined to cover within a cancer even if there is inconclusive evidence for some indications, as long as at least one indication is considered adequately supported, except for applications or uses within that cancer for which the evidence is adequate to conclude that it's not useful. And so for example my sense is, and again I'm going back to using the axilla, that PET was shown not to be adequately sensitive to use for that clinical purpose, which might lead us to a noncoverage for that specific use, but for something like monitoring response to therapy where the evidence was inadequate, we might come to a different coverage determination, so it's important to know what the committee meant by those negative votes.

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DR. MCNEIL: Okay, I think you actually had it right. I think we felt for the original three

questions, whatever it was, the data were not there, that where I indicated that the -- in many cases the data was there but because of the issue of undertreatment for example, that there were no data to suggest, the data did not suggest the use of PET in those circumstances would improve health outcomes. So you're right, say for the axillary nodes in particular, there were data, and because of the sensitivity and the specificity of the tests in those circumstances, more harm than good would be done by using the test and we thought that the data, there were a lot of studies for those indications. When we got to the question of tumor response, which is what you're asking, which was the last one, I think people agreed that it was promising and important but the data were not there, that is to say, the data showed in one study, I don't have the -- or two studies actually, from two studies the data showed that there would be undertreatment in the range of 10 to 20 percent, 10 to 17 percent, so those data showed that there would be undertreatment of patients by using this test for that purpose. But

those were only two studies.

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And there was another earlier study that was well done, I believe Rich Wahl had done it from Michigan, I think Michigan, in which the chemotherapeutic agents that were being evaluated aren't the ones that are currently --

DR. WAHL: That's not completely accurate.

DR. MCNEIL: Right, but what was studied is not exactly what is being done today.

DR. WAHL: But I thought the committee thought it was very promising because there were three or four studies also (inaudible).

DR. MCNEIL: And there was the risk of undertreatment from those same patients. So I don't know if that answers your question. There were false positives and false positives from the data that we have, and I guess the answer to your question would depend on how much you weight the results associated with errors in each of those directions.

DR. SOX: Well, we're going to take a

15-minute break at this point before coming back to discuss L-carnitine.

(Recess from 10:56 to 11:17 a.m.)

DR. SOX: We are now going to commence discussion of the findings of the Drugs, Biological and Therapeutics Panel on the use of L-carnitine

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injections in patients with end-stage renal disease, and Dr. Holohan, the chair of that panel, is going to summarize their findings.

DR. HOLOHAN: Good morning. Dr. Sox provided a critique of the absence of a written summary of the panel's findings and conclusions, and to that I plead not guilty. I had decided, Barbara and I will both do an apologia pro vita sua in this case.

DR. MCNEIL: I wasn't that literate though.

DR. HOLOHAN: We decided to wait for the transcripts of the panel, and that September would be plenty of time to get this done and distributed to the panel for their review. As some of you know, the

statutory assignment of the Veterans Administration is to act as a back-up for DoD in national emergencies, and that has eliminated all of my discretionary time, so I will present this verbally. You have the summary of the meeting minutes and you will note, those of you who are perceptive, that there was an additional member replacing the person who couldn't attend. That additional member was Dr. Emil Paganini, who is a nephrologist, who is a member of the MCAC, and he sat

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in on our panel. He is a nephrologist at the Cleveland Clinic.

Probably the most significant point to make is that the questions as initially posed to this panel were, is there adequate evidence that administration of intravenous L-carnitine is effective as a therapy to improve clinical conditions or outcomes in patients with end-stage renal diseases on hemodialysis?

And question number 2, is there adequate

evidence that the administration of intravenous L-carnitine is effective on clinical conditions or outcomes in patients with end-stage renal disease on hemodialysis? The specific clinical conditions were fairly broad and included anemia, disorders of lipid metabolism, cardiac dysfunction, muscle strength and asthenia.

And question 2.B was the same question for the oral form. I emphasize that because in fact the panel determined based on the testimony, the evidence and the reviews of the published material provided that those questions could not be answered on the basis of adequate evidence, so they chose to answer different questions.

I will stand for correction from my

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esteemed panel member at any time he so chooses to correct a statement I make.

Initially a presentation was made for the entire panel from a Dr. Chertow, who was a nephrologist from the University of California San Francisco and who is very active in developing

guidelines published under the pneumonic K-DOQI, kidney dialysis outcomes quality initiative, a multidisciplinary cross-specialty group of specialists in end-stage renal disease. And they actually addressed a year ago the use of L-carnitine for maintenance dialysis patients.

And what Dr. Chertow said, and I'm quoting from their publication on the K-DOQI nutrition and chronic renal failure document, there are insufficient data to support the routine use of L-carnitine for maintenance dialysis patients. So this group felt there were insufficient data to support its routine use for any of the proposed clinical disorders that I have mentioned above.

A review of literature was done by HCFA, by myself, and by Miss Dooley, the industry representative on the panel. The alleged benefits in the published studies, and you should have been given a matrix of the summary of published studies for each

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of the alleged clinical indications, allege that

benefits from L-carnitine were observed in decreased asthenia, fatigue, cramps, decreased muscle strength. That L-carnitine improved the lipid profile, it improved anemia, improved cardiac symptoms, and reduced arrhythmias.

In sum, a review of all of the material provided by HCFA and additional material provided by the manufacturer was not compelling to the panel. There were a number of problems with these studies. In general, the sample sizes were very small. The L-carnitine used was begin orally, intravenously and in dialysate in a mixed fashion across the studies. For every measure, every group of signs and symptoms that I have described, the results in any one cluster were positive, negative or no change. There were no group of signs and symptoms where the predominant evidence was of a benefit.

Even within the individual studies, not all measures were used on all patients. Many of the studies showed positive results based on post hoc analyses, secondary statistical analyses of the data. Very few of the studies addressed serum levels of

L-carnitine in patients who were so treated. And this is important. And I will get to the FDA letter

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that was distributed to you when I discuss the panel deliberations.

The panel concluded that the questions that I have read as posed by HCFA could not be answered, and one of the major reasons was elaborated in the letter from the Food and Drug Administration, and I will cite just a few sentences from their approval of this drug for intravenous use in ESRD patients for the prevention and treatment of carnitine deficiency.

The FDA said, clinical manifestations of carnitine deficiency generally do not ensue until levels fall to less than 20 percent of normal. They go on to say that the data support the efficacy of intravenous levo-carnitine in increasing, maintaining or increasing carnitine serum levels. However, they do not support improvements in clinical status or exercise tolerance, not do they provide convincing

evidence for decreases in BUN, creatinine, phosphorus, for increases in hematocrit, decreases in hypotensive episodes.

So basically the panel was on the horns of a dilemma. They could not answer the first question posed by HCFA, i.e., is there adequate evidence that the administration of L-carnitine is effective in

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clinical conditions or outcomes in patients with ESRD on hemodialysis because the FDA document clearly indicated that on the basis of the information provided by the manufacturer, the FDA was only willing to say that it was effective in maintaining or increasing carnitine levels. Few if any of the studies directly related serum carnitine levels to carnitine administration and improvement in the alleged outcomes.

So the panel was not confident that in fact carnitine deficiency, although they believe it existed, was defined in the published literature. They went back and recalled some of the people who gave testimony, specifically asking the question

about a definition of carnitine deficiency, and did not receive a definition satisfactory to them. At the same time they believed that the published data did include studies that showed that a subpopulation of patients did in fact appear to benefit, that is, they had either improvement in clinical status or decrease in signs and symptoms associated, putatively associated with carnitine deficiency. Because of that, their recommendations as written in the copy of the minutes you have received

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were three. First, they recommended that CMS or HCFA establish a mechanism to define carnitine deficiency in the ESRD patient population, because they believed that the published studies were adequate to show that such a condition exists. Secondly, they concluded there was adequate evidence that indicated some patients benefit from levo-carnitine but that these couldn't be identified either prospectively or retrospectively

from the published data. They recommended that Medicare establish rational guidelines that could identify this patient population. That again was a unanimous vote.

The panel did believe that the published information was adequate to conclude that there was no evidence that the route of administration, intravenous, oral or put in dialysis fluid, was likely to be or could be an important factor in the use of L-carnitine therapy.

The issue of clinical safety did not appear in any of the published literature but the manufacturer testified that they believed that the oral form uniquely could be metabolized to potentially toxic metabolites and they were asking the FDA to insert such a warning in the label of the

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oral form of carnitine. At that time and to my current knowledge, the FDA has not done so.

So again, in summary, the panel concluded that it was appropriate for CMS to establish a mechanism to develop a definition of carnitine

deficiency in the ESRD patient population. That there was evidence that some patients benefitted from the administration of levo-carnitine in any dosage form and that Medicare coverage, and I don't know if this in fact is something we're legally able to do, but the panel concluded that Medicare coverage should be provided upon establishment of rational guidelines that identify the patient population. And finally concluded that the route of administration does not appear to be a relevant factor in any benefits that may accrue from exogenous levo-carnitine.

DR. SOX: Thank you very much, Dr. Holohan. We next we will go on to comments from members of the audience. We don't have any scheduled public comment, but if anybody here would like to go to the microphone and make a comment, they should do so. Be sure to identify yourself, your affiliation and anything we need to know that might help us to interpret your work, like potential conflicts.

MR. MEHRLING: I'm Ken Merlin, the chief

operating officer for Sigma Tau, who is the manufacturer of Carnitor, and I just wanted to state that the package insert has been changed to include the precaution of extended periods of time using high doses of oral carnitine is not recommended in patients with severely limited renal function. That is in the current package insert, which has happened after our meeting.

DR. SOX: Thank you very much.

DR. HOLOHAN: Did you happen to bring copies.

MR. MEHRLING: I can have them provided.

DR. SOX: Does anybody else wish to go to the microphone to comment? In that case, it's time for members of the committee to discuss these three motions and I think just to try to be systematic about this we will go through them one by one. The first one is, CMS to establish a mechanism to define carnitine deficiency in the ESRD patient population, because there is adequate evidence that such a condition exists.

Would anybody like to raise questions

about this, or clarification, because we're going to be asked ultimately to approve this statement? Maybe I could ask a question, Tom. When

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you said establish a mechanism, what were you thinking about, a blood test or something like that?

DR. HOLOHAN: No. In fact the belief, and I stand able for correction if I misinterpret the panel's concept, I think the panel believed that in fact carnitine deficiency can and probably does exist in some patients who are end-stage renal disease patients. At the present time, there is no mechanism based on the testimony or the available published evidence that could identify and define carnitine deficiency.

The FDA defined it to a limited extent in their approval letter when they said the clinical symptoms are unlikely to occur below a serum level of 20 percent, but serum levels were not represented in the published evidence. So I think the panel was encouraging the CAg to bring together a group of

experts in end-stage renal disease and nephrology to help define for purposes of coverage determination exactly what is meant by carnitine deficiency. I don't want to keep going on, but many of the published papers presumed that signs and symptoms that patients have were ipso facto due to carnitine deficiency and the panel was very uncomfortable with accepting that.

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DR. SOX: So you're basically calling for somebody to come up with a case definition that can be used not just for coverage, but for studying the problem and identifying who has it.

DR. HOLOHAN: Yes.

DR. SOX: Bob?

DR. BROOK: I am trying to put your recommendations together with the letter from David Orloffi, from the FDA. Let me see if I understand this issue as clearly as I can. Some people are going to get this condition, everyone agrees, and there is obviously data that somebody is going to get this condition, if nothing else, through losses under

dialysis. I mean, that's the first sentence of his statement.

DR. HOLOHAN: No, he says can.

DR. BROOK: Yes, some, that's what I'm saying, some people will get this.

DR. HOLOHAN: No, he doesn't say some will, he says patients can. I don't see that as the same thing.

DR. BROOK: Okay. So some people can get this.

DR. HOLOHAN: Yes.

DR. BROOK: Okay. They've also defined

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the level, they consider that you don't get clinical manifestations of this deficiency unless the level falls to less than 20 percent of normal.

DR. HOLOHAN: That's what he says.

DR. BROOK: Now your first statement said, CMS should establish a mechanism to define it. Does that mean you didn't find evidence to accept that definition?

DR. HOLOHAN: No. What I tried to convey, perhaps inefficiently, was that few of the studies, and if you want the precise numbers I can get them for you, but few, a dramatic minority of the studies actually measured serum levels. Most of the published data presumed that signs and symptoms that patients had were due to carnitine deficiency and they were either given carnitine in a case control study, a cohort, a randomized trial, but serum levels were not available to us.

DR. BROOK: Let me see if I can follow. Why did the panel not just say, instead of CMS should establish a mechanism, why didn't they just adopt the mechanism suggested in this letter?

DR. HOLOHAN: They were not comfortable doing that. Bob, do you want to make any additional comments as to why?

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DR. BROOK: But it was discussed and people weren't comfortable, so there needs to be --

DR. HOLOHAN: It was discussed and the panelists brought up some of the people who testified

back to the microphone to ask them specific questions about whether they would accept a specific serum level, and there was general unwillingness among the people testifying, nephrologists and spokespersons for disease groups, to accept a serum level.

DR. BROOK: So what guidance would you give CMS right now to carry out, number one, how would they do it, or that's up to them?

DR. HOLOHAN: I think we -- well, you will have to ask Sean what his view was. I think the believe of the panel was that HCFA, CMS should bring together a group of people with expertise in this, some of whom testified, and develop a consensus on a definition of carnitine deficiency. That could be simply serum levels or it could be combinations of serum levels and signs and symptoms, but probably not just the presence of signs and symptoms.

DR. BROOK: Okay. Now can I just ask one other question. Regarding number 2, there is another really very strong statement in this letter from the FDA, it would be therefore, unethical to subject

patients to the risk and discomforts of frank carnitine deficiency in a study designed to assess the clinical benefit of supplementation because of the safety of supplementation.

DR. HOLOHAN: Okay.

DR. BROOK: So when you said, and when you reviewed these studies and showed that in all patients in ESRD, the routine use shows, you made a comment that there was no evidence to support that routine use would benefit people with any of these outcomes.

DR. HOLOHAN: That's what the Kidney Dialysis Outcomes Quality Initiative said.

DR. BROOK: Okay. Now what I don't --

DR. HOLOHAN: The panel concluded that on the basis of the published data, one could not conclude with any at degree of certainty that supplementation with levo-carnitine in any form, PO, IV or in the dialysate, significantly improved the clusters and groups of signs and symptoms that had been alleged by the authors of those papers to be due

to carnitine deficiency, i.e., anemia, weakness, asthenia, cramps.

DR. BROOK: Could not?

DR. HOLOHAN: Correct.

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DR. BROOK: Okay. So when you say there is adequate evidence that some people benefit, the language in here is it would be unethical to take -- there's go to be in this population a group of people can develop, so you say number one, that there are people, and so if you have these people in this population, presumably they would benefit from supplementation, but what is the evidence? Is the evidence based on animal models? What is the evidence based upon, because here it says it's unethical to randomize people. What --

DR. HOLOHAN: I agree with that, but I don't see anything about randomizing people.

DR. BROOK: No. You say there's adequate evidence. And you just said that the studies didn't show that, and so what I'm indicating is where does

that evidence come from?
DR. SOX: Well, let's -- I'm trying --
Bob, if you could defer that question until we get through the first one.
DR. BROOK: Okay. I was just trying to put them together in some sense.
DR. HOLOHAN: I think I can answer that quickly. When I was summarizing the clinical trials, I pointed out that the panel concluded that in some

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of the trials there appeared to be a subgroup of patients, mostly identifiable retrospectively, that did appear to have significant improvements in signs and symptoms, be it anemia, muscle weakness, asthenia, cramps. The panel believed, most of the panel believed that in fact there was a strong suggestion that there may be a minority, a subgroup of patients who might benefit that at the present time cannot be easily prospectively identified.
DR. SOX: Dr. Whyte is going to try to provide some information to help us.
DR. WHYTE: I'm John Whyte. I'm one of

the physicians in the coverage group. What I wanted to clarify on point one was Dr. Holohan had mentioned how there was modification of the questions that we originally presented to the panel, and we were not planning to ask as one of the questions, how do we define carnitine deficiency, so we did not provide information as to what we would consider carnitine deficiency.

So that's why you may see the panel talking about that they do not feel that there was adequate evidence to define carnitine deficiency and that would have been because we didn't provide that information.

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We have had multiple discussions with the FDA as well as others, and I am not prepared today to talk where we are in decision making, but certainly we feel at a staff level that we have enough information to define carnitine deficiency. So I just wanted to provide as background the reason why you may have this point is because we didn't provide

the information, because we weren't planning to answer that question.

DR. HOLOHAN: Right. I think, just to elaborate, the panelists believed that most of the published data presumed that because patients were on chronic dialysis and it was not unreasonable to believe that you can remove carnitine in hemodialysis, there was a presumption on the part of the authors of the papers that in fact the patients subject to their study had carnitine deficiency. And in looking at the totality of the evidence, the panel was unwilling to make that leap of fate, particularly in view of the FDA approval letter that talked about a serum level which rarely appeared in any of the published studies.

DR. SOX: Alan?

DR. GARBER: I think one of the reasons this is a little bit hard to sort through is first of

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all, I think the recommendation 1 should be subsumed under recommendation 2, that is, identifying subgroups who would benefit. The issue is not really

whether the carnitine deficiency per se causes the symptoms; the issue is does carnitine supplementation help these symptoms. And from what Tom has said, it may not be that clear that you can use the carnitine level to determine who is most likely to benefit. It may be there should be some other selection criteria, and to answer number 1, that CMS should develop criteria based on carnitine is to presuppose that the carnitine level defines the subgroups who benefit. And given that some of these trials didn't even measure the carnitine level, not to mention that they didn't clearly and consistently demonstrate benefit, it seems to be jumping too quickly to a conclusion that carnitine is the issue.

And I have to admit, I am also confused by the FDA letter, where it says the clinical manifestations do not ensue until levels fall to less than 20 percent of normal, but then the clinical team leader's note at the bottom basically says that there is no evidence that carnitine supplementation improves symptoms, what it does is raise carnitine

levels. So how they, the FDA has given a rather

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tepid approval to this, saying that it's like giving sodium may raise serum sodium levels if there is some problem with your auto regulation.

But it seems to me the first question has to be number 2, and I don't see how CMS can be expected to develop carnitine criteria unless they know that the carnitine level defines subgroups who would benefit.

DR. WHYTE: I don't disagree with that statement. The only point that I wanted to make was to make sure people knew, part of the reason why they didn't have adequate evidence addressing point 1 is because we didn't provide that information, and that's the point that I wanted to make clear.

DR. GARBER: But does it exist?

DR. WHYTE: There is a body of literature that discusses exactly those points that you talked about. We didn't provide all of that information to the panel, because that originally was not one of the issues that the panel was going to address.

DR. SOX: Any other discussion on the first item? I hope nobody is planning on rewriting these recommendations too severely, unless it really looks important.

Let's go on then to number 2, there is

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adequate evidence that indicates that some patients benefit from L-carnitine. Upon establishment of rational guidelines that identify this patient population, Medicare coverage should be provided. Speaking for myself in reviewing the HCFA review of all that evidence, I was hard pressed to, I was surprised to see this statement, because it looked to me as if studies weren't consistent in their results, the effect size were relatively small, as you already pointed out, Tom, studies often involved relatively few patients, and so I thought, I'm surprised that the panel actually made this statement. So maybe you would like to comment on that and there may be other things that we will also want to talk about with this statement, but let's

start with that one.

DR. HOLOHAN: Well, I'm not going to philosophically disagree with you, but let me put myself in the loafers of one of the panel members or any of the panel members. If you look at the chart on the effect of carnitine on EPO requirements, I only found three studies that were fairly recently published, and one showed no change, but two showed EPO requirements decreasing, in one case in 8 of 19 experimental group of patients, and in the second

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study EPO requirements decreasing in 7 of 13. I believe that the panel members concluded from these, and studies in your charts on exercise capacity and strength, asthenia symptoms, et cetera, that there could be a pony under all of this other material, and that perhaps if patients were selected well prospectively, you could have identified which 8 of the 19 did in fact benefit from levo-carnitine. I think there were enough studies where small proportions of patients showed in some cases not unimpressive improvements in either hematocrit,

exercise capacity, reduction in fatigue, et cetera, and they were unwilling to cast aside the possibility that there was a potentially identifiable group of patients who might benefit.

Have I misstated the belief of the panel?

DR. MURRAY: I wasn't there.

DR HOLOHAN: Oh, I'm sorry.

DR. FRANCIS: I wasn't there, but can I just understand this. There was adequate evidence that someone benefits but inadequate evidence as to which patients those are, or inadequate evidence about our ability to identify prospectively?

DR. HOLOHAN: I have read through the transcript several times and I don't think anybody on

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the panel ever quite phrased it that way. I think they believed that the published data included studies that showed that small proportions of patients showed a benefit, that the data were insufficient to conclude that it should routinely be used on all ESRD patients, but maybe, just maybe it's

possible to identify prospectively those people who would benefit. Maybe this benefit in 7 out of 13 wasn't just chance.

DR. SOX: Wade, I think you were next.

DR. AUBRY: I'm a little bit confused about the dosages, and maybe this is sort of getting ahead of the question, but if the panel is making a recommendation on coverage, that would include not only patient selection criteria but also some recommendations for dosage. It seems like these studies have quite a variability of dosage.

DR. HOLOHAN: You are a master of understatement.

DR. AUBRY: And so I'm totally unclear as to what would be an appropriate, you know, therapeutic dose. Even these EPO studies show variability.

DR. SOX: Alan, I think you were next.

DR. GARBER: Well, I don't think that the

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fact that only 8 of 19 or 7 of 13 benefitted means that this has to be targeted. If this is an

important benefit to reduce EPO requirements, then these studies seem to establish it. So I don't think we could hope to in every study to find the subgroup that has the greatest benefit. The question is, is this statistically significant and if the answer is yes, well, this is related to that question, was this the primary end point for these studies, and do we take this seriously and were there offsetting adverse effect.

But the issue in interpreting these studies, yes, these were significant and yes, there was a prospectively defined end point, and there were not offsetting adverse effects, then the real issue becomes how do you duplicate the population that was entered in these studies, not so much how do you find the subgroups within the study that got the greatest benefit. Because 50 percent of the people got a reduction and the mean reduction was about a third for the experimental group, so that sounds like a fairly large reduction if you think EPO requirements is an important end point.

DR. SOX: Other comments? Sean.

DR. TUNIS: This is sort of related to

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Alan's point on the EPO requirements, but also Dr. Holohan wanted to clarify with you was that the original questions that were posed to the panel actually broke down into the specific indications of whether there was adequate evidence that supplementation was effective in EPO resistant anemia and fatigue, in muscle cramps, et cetera, individually broken down; is that right, John?

DR. WHYTE: That's correct.

DR. TUNIS: So I believe again, correct me if I'm wrong, but I believe that the panel decided not to answer those questions specifically because in part they felt that taken individually, for no single indication did they feel that the evidence met this adequacy criteria. And again, I'm posing that as a question as opposed to, because that's my recollection, including the review of the evidence on EPO resistant anemia. Tom, is that your recollection, or anyone else?

DR. HOLOHAN: It is.
DR. TUNIS: So I think that then, that's what led to sort of the second recommendation of the panel which is while no individual indication did they feel that the evidence rose to the level of adequacy, they felt that in aggregate there was

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something there. I don't know if anyone talked about a pony specifically, but that there was something there. And that's my own recollection of the discussion, but if John or anyone else from Sigma Tau or others had a different view, we should hear about that as well.
DR. BROOK: I'm a little confused. Why did the panel not just answer the questions no and then go on to other -- I'm trying to deal with process here and improve the process. There were a few questions that were posed. It sounds like you answered no to the evidence questions that Sean just talked about; is that correct?
DR. HOLOHAN: Yes.

DR. BROOK: Why are they not in the recommendations of the panel? Why did the panel not vote on them?

DR. TUNIS: I think the panel asked not to vote on them.

DR. BROOK: Well, I'm really wondering about the process. We're being asked to provide an advisory function to HCFA. I mean, I thought Rand was the only person that came in and changed the entire question and context, and then wondered why we never got any business.

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(Laughter.)

I mean, the question here is that we're asked to answer some questions, and I'm being serious about this. Is there part of the minutes of this thing that ought to be brought forth in the summary here of what was proposed, that would state that either the panel did not -- it was obvious by intent or consent that the evidence wasn't there to answer any of these questions, and therefore we can be confident that the answers to the original questions

that CMS proposed is no.

DR. TUNIS: Well, let me just make one comment in terms of the process, and maybe someone can answer the question about the sense of the minutes. But if you recall, there was a previous episode in which CMS diligently stuck to the questions and forced the panel to answer them with an unsatisfactory result as well, which was that the panel sort of rebelled or made their feelings known in terms of the feeling that the questions were too constrained. Maybe this is deviation too far in the other direction, but the feeling was we had a bad result from forcing questions on the panel that they felt in some way --

DR. BROOK: I'm not arguing that they

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can't answer other questions, but we saw the problem that occurs when you begin to answer other questions if the evidence has not been summarized.

DR. TUNIS: Right.

DR. BROOK: And what I'm trying to get at

is the process here but before we get -- the first issue here was, it sounds like they came close to suggesting that the questions, regardless of whether they're good or bad questions, there was not evidence to answer them, and the evidence was insufficient.

DR. TUNIS: That's my recollection, again.

Tom, do you want to talk about that?

DR. BROOK: And then John said that in answer to question number 1, which the panel recommended, he was concerned to get on the record that the reason that there may be, there may be more evidence to answer question 1 than currently the panel had available when they deliberated. And I just want to, I mean, there seems to be a process problem here. I have no problem with these recommendations. I mean what I'm trying to get at is the process problem.

Now on recommendation 2, I have another question. If they voted that there is adequate evidence that some patients would benefit, don't they

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need to state as they did on the first panel, the

other panel, what's that based upon. It sounds like it's based upon hunches that within the trials there are subgroups of people that seem to benefit, but there was not a subgroup statistically specific analysis to support that, but there is clinical logic to support that, and that's the reason that they concluded that there is adequate evidence. I mean, I am just trying to lay out what the rationale, what they believe the level of evidence or effectiveness was in terms of to say that there is adequate evidence.

DR. HOLOHAN: Let me read a few statements from our designated nephrologist panel member that may give you a flavor of that. Dr. Paganini says, I have been sort of impressed and unimpressed straight through. I came in with a fairly open mind. In the clinic where I practice there are some folks who use it and some folks who don't, and it seems to be used mostly in subgroups of patients that are on dialysis that you tried everything else and why not try this. In reviewing the literature, I was relatively

unimpressed with the outcomes that were purported. However, he goes on to say in a discussion with one of the people testifying, no, I think what

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I'm trying to do, honestly, Joel, is I think that carnitine may in fact have some significant improvement effect in some patients, and I'm trying to get a handle on who those patients are. And by what you listed here, and I know this is not supposed to be a debate, but what you listed here, I can list for just about all the patients I have ever come in contact with on dialysis, and yet the literature doesn't seem to support that. So I'm just trying to get a handle on who that subgroup might be that would truly benefit and whether or not there is information out there.

DR. BROOK: Did anyone question why the FDA said it would be unethical to actually do a study to answer the question, to find a subgroup? This statement says that -- I mean, if this went through a human substance committee, we are in deep doo-doo, because this statement says that what you have told

me is that nobody has prospectively identified a subgroup of patients that have a higher likelihood of benefitting from it, and then randomizing them to look at some of these outcomes that HCFA was interested in understanding the effect of. And when you do it across the whole board, you find wishy-washy results. I mean, that's sort of what I

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heard you say, and everyone agreed to that. And then in light of that, I find this thing very disturbing, that the FDA says because this is a basic -- where it -- it's unethical to subject patients to the risk and discomforts of frank carnitine deficiency in a study designed to assess the clinical benefit of this supplementation because it's an essential metabolic intermediate and that regardless of cause can be a serious and life threatening condition. Now, is there evidence that, and that's the part that I'm missing, is there evidence that if this value or something gets low enough that this is a life threatening condition?

DR. SOX: John?

DR. WHYTE: I missed part of your question as I was trying to find the original questions, but the comments that I wanted to make, Dr. Brook, relating to issues of process from a staff level is we provided the panel with a lot of information and as Dr. Holohan pointed out, we broke it up by certain types of indications. And part of your issues relating to process, that may be too many questions for the panel to answer for each particular indication. Whatever the point is about that, what I have to emphasize is that the panel did not vote on

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those questions and it probably should not be presumed by this committee that by not voting on those questions they voted no or said anything about the adequacy of the evidence.

In terms of the information we provided to the panel and what we were trying to sort out, the issues are similar to what Dr. Garber mentioned a few minutes ago about how levels correlate with symptoms and what's the appropriate measure. Just from a

staff level, part of the issue relating to levels is what we want to consider. If we operationalize a policy, there are some issues of a level helps us to have some indication of how symptoms improve. But the important point that I wanted to make, again, was that it shouldn't be assumed that because they didn't vote on the questions, that they felt that there was not adequate evidence to answer those questions.

DR. SOX: Daisy.

DR. ALFORD-SMITH: I still don't quite understand how questions are presented to a panel, and they fail to respond in any way.

DR. WHYTE: I can tell you, Dr. Smith, this isn't the first time, as Dr. Tunis pointed out, that it's happened. It's happened on other panels as

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well, and part of what we tried to do is to give the panels flexibility based on the discussions that happen at the panel meeting. Just to tell you process from a staff level internally, we think about

what the questions need to be, and we develop the questions in consultation with the chair and the vice chair of the panel, and then we present the questions. Sometimes during the discussion of the meeting other points are brought up, and that's partly what happened at this meeting, that the panel decides to modify them.

And you bring up the point, maybe we should force the panel to vote on the questions we originally asked, but as Dr. Tunis has pointed out, that has not always been optimal either.

DR. ALFORD-SMITH: Here is a second part of the question. Based upon the responses to the questions that they chose to answer, did that prove to be beneficial to you?

DR. WHYTE: Since the panel meeting, we have continued to do a lot of research on the topic. And what I can tell you, it was beneficial because what the panel has basically said is they want us to define what is carnitine deficiency, and that is something that we were working on prior to submitting

these questions to the panel, so we are continuing to work on carnitine deficiency, and what I would say is that the panel has sensitized us to the importance of that. As Dr. Garber points out, there may be more than one way to identify patients with carnitine deficiency but not something that we're doing.

And then the other point we talk about is the second point about there's adequate evidence that some patients might benefit, because they viewed it in the aggregate that some patients benefit, and that we needed to more work based on the literature, or perhaps presentation of data, to identify that patient population, and that is something that we're doing.

So I think these recommendations actually are things that we have been working on since the panel meeting after getting a sense of where the panel thought we should be going.

DR. ALFORD-SMITH: Last question.

DR. WHYTE: Sure.

DR. ALFORD-SMITH: Again, once we respond

to their recommendations, should they be able to answer the original questions?

DR. WHYTE: I think they will answer the original questions.

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DR. ALFORD-SMITH: Thank you.

DR. SOX: Randel?

MS. RICHNER: In terms of process, I think this discussion both from the PET discussions earlier and now this, once again, it really highlights how we have to work on process this afternoon, and I'm hoping that we will have a chance to do that. I have actually asked Connie to make copies again of the guidelines so we can go back to the issue which is very fundamental to all of this, is what questions need to be asked of the panel and how does that process work and who has input into those questions along the way, and how are these defined. And then further, in terms of what are -- if Sean, the Executive Committee is sort of stuck in this conundrum of having to do the ratification of the panel discussions until we can fix BIPA and so

that we don't have to go through ratification anymore, then Leslie and I talked at break, what is our remit then in terms of ratifying their decisions? Is it about looking again at the evidence or is it about how the process went within the committee and how they made their decisions? Because we're going to end up going into a spiral again on this carnitine issue if we're looking at the evidence, or if we're

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looking at the process. So Sean, we need your guidance here.

DR. SOX: Well once -- we're going to stop having any sort of approval function after this meeting, but we still have a function to oversee the process the panels undertake and to be sure that they follow process, that they report in a way that people can understand the logic that links the evidence to their conclusions, and generally to have an oversight function that I hope that we are very active about, because I think it's an very important role for this group here. And I agree with you, I think there are

some holes here, and that there is a job for us to do.

This statement here which at least I didn't see until today, doesn't give any kind of flavor for the discussion of what the original questions were, why they decided to abandon those questions, which I think is their privilege. We may criticize that on the basis of their reasoning for abandoning them, but we're left with a very skeleton document that doesn't give any sense of either the process or really the rationale for the final recommendations, which we're learning during this discussion but personally I think we ought to be

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seeing them before we get to the meeting. John.

DR. FERGUSON: As some of you know, I was director of the consensus program the NIH for 11 years and the program has existed for 25 now. And the crucial thing besides the composition of the panel was the formulation of the questions which the panel was asked to address. And the planning committees always spent nearly a day, at least half a

day formulating those questions, and that was a fairly high powered group. And every panel, virtually everyone wanted to change the questions or at least some of the questions once they got to the consensus conference, and we made it a standard rule that the questions could not be changed.

Now, I would suggest that formulating the questions for which these panels are going to be asked to address is a very very important thing and the wording is terribly important, and that possibly some of our input, certainly the panel chair's input could be, and getting a review of those questions once CMS has formulated them.

DR. TUNIS: I would just emphasize, HCFA spends a tremendous amount of time working on these questions. But as you know, part of the reason we refer a small percentage of issues to the coverage

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advisory committee is that we find the issues to be complex enough that in fact we cannot guarantee that the questions are perfectly formulated. If we could,

we probably wouldn't need to come to MCAC with the issue in the first place.

In the case of the PET for breast cancer, I think the panel made a very intelligent refinement of a question by breaking it into two pieces and that was arrived at by a careful review and discussion of the evidence that is the function of the MCAC in the first place. So I don't think there is ever going to be a way that we can guarantee, no matter how careful the process, that we will get the questions perfectly.

And I don't agree that we should never consider changing the questions once we get there, because again, it assumes that we knew more going into the meeting that than we have learned during the meeting. And this isn't the NIH consensus process, this is a coverage advisory committee, it's a different process, it has a different function. So you know, I think that part of what is going on here is part of the process that needs to go on, which is you know, dealing with difficult issues and a difficult process.

So you know, whether or not this is the way it should have worked and that we should have changed these questions, is obviously open to discussion.

What I also do want to point out is in terms of the function of the Executive Committee related to the panels, it was a legal requirement that we have an executive committee reporting to CMS, so the purely technical reason behind it was that panels would report to the Executive Committee out of necessity, not because anybody thought that was the perfect process. Since we have the ratification function we have to figure out what to do with it, and I think you need to understand that we take the input and discussion of the panels and even if the Executive Committee completely came to a different conclusion doesn't mean that we don't pay attention to what the panel said. We take into account what the Executive Committee says in addition to what the panel says.

So it's all, you know, recommendatory or whatever the word is, advisory, that's a better word, thank you. And so I just don't think you have to worry quite so much about, you know, whether this is an undermining of the panels. It's all additive to

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the input that we get from the panels.

DR. SOX: Yeah, but transparency is important in public affairs and when you get a document that is so opaque as this one, we're not, it's our job to be sure that panels are accountable to us and the public, and part of that is explaining their reasoning if they go off in a different direction.

MS. RICHNER: There is just one thing I want to add. The problem is that if we should send the decision back to the panel once again, we have a time issue, and that could prolong this process exponentially. I'm sure Barbara was a little concerned that this was going to go back to panel, as we all were, so we have to take that into account as well, Sean. I agree, and I respect that you're

taking all of this in as an advisory kind of issue, but process could lead to a very very long time associated with this, so we have to be very cognizant of what we recommend and advise, and how we ratify this.

DR. SOX: I just want to remind us that while we're getting off into important general discussion of process, that we aren't going to go to lunch until we deal with these recommendations, so I

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do want to move us back fairly quickly to recommendation number 2 and whether it's phrased, you know, whether we should have it stand as it is. But why don't we take a couple more questions on the general issue.

DR. BROOK: Hal, let me just make two comments. The first is that what Barbara's group did was to split a question and then vote on both parts of it, and that's fine, and we know how to make that in the record transparent. I can't tell from number 2 whether what Tom's group did was to take the

individual indicators of respiratory, exercise tolerance, EPO requirements and others, and lump them together in this vague group called patients benefit because they couldn't answer the individual questions and try to lump them together. I am assuming that's what they did here, because it would be nice if that was transparent.

Now, what's missing from this is the statement of how they judged adequate evidence, and I think we have to vote no, given our process on anything that says there is adequate evidence without the question that Barbara's panel was forced to vote on, which was, what's the effect, how did they get to that level, what's the evidence based upon, some

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statement in the minutes to make it transparent. We seem to approve without discussion anything that says there is insufficient evidence or inadequate, we don't spend a lot of time on those things.

So I'm wondering whether, Tom, there is stuff in the minutes, or the transcripts, that you can add something to this that would say we based

adequacy on the following, so that there is something here that would explain how you judged adequacy of evidence against the process that we put together. Can we add two or three sentences here?

DR. HOLOHAN: It's possible, but I can't guarantee that that would be satisfactory.

DR. SOX: Maybe I can say it a little bit differently than Bob. Adequate ought to mean more or less the same thing regardless of which panel is reporting on which issue, and if we allow adequate to take on whatever meaning the panel chooses to impose on it in the course of a discussion, you know, we don't have a good process. And you can say adequate and then give qualifiers that indicate it really isn't quite up to the usual standard, but we're going to have to learn how to be consistent from panel to panel and discussion to discussion in how we use really important words like adequate evidence.

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DR. HOLOHAN: The transcript does reflect my reading the summary of the definition of adequate

evidence based on the material the Executive Committee provided. I'm not sure you can follow that trail clearly through to these conclusions.

DR. SOX: Let's talk about this. Do we simply want to leave this stand? Maybe I can just raise a question, Tom. Was the implication that the evidence was good enough so that HCFA should go ahead and provide coverage as soon as the guidelines are created without any sort of further consideration of for example, your ability to identify which population would benefit?

DR. HOLOHAN: Well, I thought that was part and parcel of number 2, that establishment of rational guidelines that identified this patient population, i.e., those patients who would benefit, Medicare coverage should be provided.

DR. SOX: And that's sort of based on things like 8 out of 17 and 9 out of 18 patients benefitted. Yes?

MR. MEHRLING: In going through the minutes, and I appreciate the difficulty in identifying this, but Dr. Paganini actually tried to

address that specific issue, and he started, you

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know, I think you stated correctly what I wanted to do. I'm very concerned that if we take all the data that has been presented and has been shown and has been published, that there are some very significant responders in that population that carry the mean of those studies. And if we say that there is no indication that carnitine does any good to anybody based on those studies which are very weak, we are going to eliminate a significant number, albeit not a large proportion, but still a significant number of folks that do respond to this therapy and have had dramatic responses, not only -- and it goes on. What he was really doing was showing that there were some studies where the mean was carried by a small number, and they wanted to get at identifying better who those patients were, although the studies were statistically significant, and that was part of the discussion.

DR. BROOK: Can I -- what I don't

understand is if you take a group of hypertensive patients and you treat them, not all of them are going to benefit from hypertension therapy but the studies would show that some do, and we then approve it for everybody because we don't know up front which of these will benefit, because we can't tell which

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person with the 95 diastolic will benefit from this drug, and we would probably have to give 100 people the drug to have one person benefit.

Now what I'm asking, from the data that you reviewed, the panel process, when you reviewed these studies, did you believe that there was a statistical case made using our definition of evidence, that when they gave this group of patients this drug that any of these, I don't care, any, all, collectively, singularly, that any of these benefits actually were different, indicating that there is some action in at least some subset of this population by providing this supplement?

I mean, the way you presented it, Tom, I got the sense that you didn't believe that, and

that's what really shook me up.
DR. HOLOHAN: Well, you've asked two things. You said when you looked at all of these data for all of these indications, did you believe it was beneficial and the answer was no, the panel generally concluded that the evidence was insufficient for treatment or prevention of any of those signs or symptoms. But then you went on to say but did you believe there was a subset, and I think several members of the panel believed there was, as I

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quoted Dr. Paganini's statement.
DR. BROOK: That was shown by the data, not that was shown by, I treated three people and they benefitted and the symptoms disappeared. I understand that. I don't understand -- I mean, do you believe that there was a subset, or is the subset so small, like one in a thousand, that the sample size just overwhelms it with noise and the studies have not been able to pick it up?
I don't understand what the panel believed

about the evidence. Once you tell me that, then we can understand when you meant here.

DR. HOLOHAN: I think that was encapsulated in -- do you want to read Dr. Paganini's statement again? I think that was generally accepted by most of the panel members.

DR. BROOK: So let me go through this, that the proportion of people is so small that the evidence for the studies as a whole, all of the studies doesn't support it.

DR. HOLOHAN: Are not compelling.

DR. BROOK: And the reason it doesn't support this is there are so many people in this group that don't benefit from the supplementation, and therefore the noise of just having those people

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there overshadows this small effect that clinicians have observed in a few very seriously deficient patients who get better with this therapy, and that that's the belief, that was how the evidence was put together by the panel.

MR. MEHRLING: Dr. Paganini was not

stating that, and I don't mean to correct but to clarify, that the mean is carried by the responders, and that you would have a 7 of 15, or a 4 of 15 respond, and the change would be statistically significant as a group.

(Inaudible colloquy, people speaking at same time.)

DR. GARBER: He's just saying that the benefits are skewed and so the problem with that of course, is that when you say the benefits are skewed, that's kind of like saying that people who do well with surgery are going to do well with surgery. You're defining by the end point rather than, unless you can prospectively identify that skewed group, because the benefit is not really useful.

DR. BROOK: If the drug is completely safe, Alan, I beg to differ. If this is a really safe drug and you don't have to identify who's benefitting if in the whole population basically the

mean level of the population is different. Just like

you treat everyone with diastolics of 95 even though we don't know who benefits from them or not.

(Inaudible colloquy, people speaking at same time.)

DR. GARBER: But whether it's skewed or not, if you thought that this was a net beneficial on an average group of population, then you would say yes, it's a good thing. You can only take advantage of the skewness if you can prospectively identify the subgroup.

DR. BROOK: Absolutely. Like HCFA has done with oxygen lower than 55, or whatever the value is, we give them home oxygen, or if you get epogen, if the value is below something on a hematocrit or anemia, because we believe that those people benefitted more. All I'm saying here is that you don't, I mean, did you find statistical evidence, and I'm pushing it. What I don't here from you is that the statistical case was actually made that any of these studies prospectively identified a subgroup and that in that subgroup it benefitted. On the other hand, the stuff that Alan quoted suggested that there

was responders in terms of epogen. Is that correct? And if that's correct, then we have a benefit and we

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have a study, and we have evidence, and if we accept that as a benefit, then we can accept recommendation number 2.

DR. SOX: If the evidence that epogen requirements are reduced is a statistically significant observation in a recently constituted patient sample then we can probably accept the truth of number 2. We don't have to identify who they are.

DR. GARBER: Well, they have to correspond to populations in those studies.

DR. SOX: Right. But at least I haven't heard the level of evidence and the level of detail in this doesn't really tell me in small numbers whether this was a real, or consistent with a chance fluctuation.

Would you like to identify yourself?

DR. SCHREIBER: I'm Dr. Brian Schreiber. I'm an assistant clinical professor of nephrology at

Medical College of Wisconsin. I also am a clinical nephrologist in charge of 300 dialysis patients in Wisconsin, and I also consult for Sigma Tau because I studied carnitine for many years, have published on it and researched carnitine.

I apologize for not speaking sooner. I don't really know the process here, but I do want to

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just -- I was at the meeting, I do want to help clarify some questions that have been raised.

DR. SOX: I do want you to focus on question number 2.

DR. SCHREIBER: Absolutely. First of all, the actual -- you know, this question, was there evidence, was there not evidence, the actual motion that was actually passed, was voted on and passed actually contained the words that there was adequate evidence, adequate evidence that certain subgroups of ESRD patients on dialysis would benefit from administration of levo-carnitine. Now, exactly what Dr. Garber said is what was found.

See, the hearings, the panel actually did

a very detailed look at each of these studies. The P values were significant in many of these studies. A pattern emerged however, where in many of these studies there were dramatic responders and it was the feeling of many people that these dramatic responders were accounting for the positive P values. Yes, they were positive P values, they were statistically significant. And we, what happened was I got the sense frankly, this was a very good panel and Dr. Holohan ran this like the best med school professor I have ever seen. He had people looking

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deeper than the questions were asked. And what happened was people said okay, yes, it's statistically significant, the P values are good, but they also are skewed as a very dramatic group. So shouldn't we say that we should try to identify this group, that to get this it would be better if we could prospectively identify this group, and that's what the conclusion was. It was not saying that the P values were not significant, it was

acknowledging there was a clustering of dramatic responders. Let's tell HCFA to go to work and find out how to maximize the chance of getting that cluster, and that's what the recommendation was in regards to 2.

Can I say one thing about levels please?

As far as the levels in the FDA, there is some confusion there because the FDA's statement on levels, and this is why the people were a little unclear on levels, refers to primary carnitine deficiency, a condition in children principally who are unable to metabolize carnitine. These were not dialysis patients, so the level of 20 percent. They found, the reason the FDA actually approved carnitine is that they found that the mean level between dialyses approximated that, and so people said well,

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should we just talk about a level?

What Dr. Kopple, who is one of the eminent people in nephrology and metabolism within nephrology pointed out, and many nephrologists believe, that you have to look at carnitine deficiency and carnitine

insufficiency, meaning you have to balance the carnitine according to how many fatty acids you have to metabolize.

And that's what was raised to the committee, that you can't necessarily take a level that has been examined in primary carnitine deficiency in children with healthy kidneys, and generalize that to the dialysis population. And they felt, again, that we had to look deeper at that, because the metabolic needs of the dialysis patients were different. So that's why it was sent back to HCFA, to say okay, you get together some smart people in nephrology and you tell us in dialysis patients how you would define that, because the population the FDA was talking about in terms of its level statement was different. Does that make it any clearer?

DR. SOX: Thank you.

DR. GARBER: I'm just wondering, John Whyte told us that they really didn't do an extensive look at the literature on levels of carnitine and so

on. Is there a literature that we could turn to that hasn't been reviewed by MCAC or by the panel that would help you to identify that subgroup of high responders if you want to call it that, that really respond well to carnitine supplementation? Is there a literature, or would this be just the opinions of experienced clinicians not directly supported by formal studies.

DR. SCHREIBER: That's a good question. There is not a dedicated literature to that. However, what we did and what took place actually at Dr. Holohan's direction was looking at the studies and looking at the characteristics of studies that had more positive outcomes and more negative outcomes. And what the panel did was then look at the characteristics of the patients, whether the condition existed and was clearly defined, whether alternative explanations for the same clinical condition had been looked at, and we compared those things. And so it was really taking from the studies, trying to extrapolate that group. But as far as studies where they started

out prospectively with that group, that is within those studies, a lot of that information is within those studies, and that's where the meeting was

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directed, to try to extrapolate that, and that's where CMS has also been directing its attention, to try to extrapolate, because there's a lot of data on carnitine, it has been around a long time, and so to extrapolate from the data that's there the best ways to define this group. Within the data that's there, you can make those extrapolations, but it's contained within the greater literature.

DR. SOX: I'm hoping that a story is emerging that is making us more comfortable with number 2, I'm not sure that is true, but I think we do need to move on, so if we could have a few wrap-up comments on number 2, I don't think we're going to learn much more to help us on this. Bob, and then Bob.

DR. BROOK: If I could just ask one question about number 2. Did the panel decide, the

first part is adequate evidence that some patients would benefit. What I'm asking is did the panel discuss when they did this asking the question that because of the uncertainty of this protocol of identifying patients that Medicare, that CMS should actually set up number 1 and test it, as opposed to a demand that everyone gets full coverage to it? Was there some discussion of that?

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I'm just trying to get the intent of the panel out of this, because you go from this to that once we have this, everyone ought to be covered. Do you think it's unethical, or did the panel discuss this, that it would be reasonable once you develop this protocol to randomize people? These look like very short-term outcomes in terms of EPO, hematocrits and hemoglobins, you know, is this something that everybody ought to be covered that you felt at the moment, or how did the panel get from the first sentence to the second sentence, that Medicare coverage should be provided to everybody?

DR. HOLOHAN: Let me think about that

nonsuccinct question. The panel never reached to the issue of whether research should be done, either sponsored by HCFA or not, to identify that group of patients. What the panel believed was that until and unless there were reasonably sufficient information that could a priori identify patients who would be likely to benefit, that Medicare should not routinely provide this as a benefit to all patients, some of whom might potentially benefit.

DR. BROOK: I understand that, but how about the ones, let's say tomorrow they come up with this mechanism, define this mechanism. I just want

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to make sure, the intent of the panel was that once CMS does that, that the advice to CMS would be to recommend coverage for everyone that falls into that guideline.

DR. HOLOHAN: Correct.

DR. BROOK: Without any further testing. You didn't think there was a need for any further scientific data, based on --

DR. HOLOHAN: Now, the premise as I understand it that you have proposed is if in fact one could reliably identify those patients who would benefit, and the panel believed that it was possible to do that, that for those patients coverage should be provided. I would think intrinsic in that is the belief that the mechanism for identifying them would be less than accurate, so why would you have to study something?

DR. BROOK: So you believe that there is such a mechanism that can be done, the data supports all that and that's the logic behind this recommendation. I just want to be clear about that, the panel in reviewing the evidence believes that CMS can do this, and once it's done, it would be unethical really to randomize these patients or to study it any further, it's time to cover them.

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DR. HOLOHAN: I don't think the panel overtly or covertly expressed the level of confidence in CMS's probability of success in establishing these guidelines but the panel thought that it was a worthy

attempt.

DR. BROOK: So, I move we ratify all three motions.

DR. AUBRY: Second.

DR. FRANCIS: I need to understand 3.

DR. SOX: Okay. We're on to 3 unless there is something big on number 2. Wade.

DR. AUBRY: This is a point of clarification. Was it the intent of the panel when you talked about rational guidelines that identify the patient population, you also were including in that rational guidelines for therapeutic dose?

DR. HOLOHAN: No, we did not address the dose. If you look at the little matrix that I handed out and just looked at the dosage, routes of administration and dosages, it was impossible. They were all over the chart.

DR. AUBRY: Well, I'm not sure this needs to be in a motion, but I would hope that CMS when it does its review would also try to develop some rational guidelines for dosage as well, but I'm not

making a motion.

DR. SOX: Let's go on to number 3, Leslie.

DR. FRANCIS: Yeah. I just heard two different things and I want clarification. Does 3 say the evidence is sufficient that the route of administration doesn't matter, or does 3 say the evidence is insufficient that it does, and I thought I heard you say both of these.

DR. HOLOHAN: Well, what this says is what it says.

DR. FRANCIS: So it's insufficient evidence about whether the route matters?

DR. HOLOHAN: Yes.

DR. FRANCIS: So we would want to get more evidence about whether it does.

Dr. HOLOHAN: But we didn't answer that question.

DR. SOX: Any other questions about number 3? In that case I think it's time for a motion and a vote.

MS. ANDERSON: We actually have a motion

on the floor, Dr. Brook's motion that we vote on all three, and Dr. Aubry has seconded it.

DR. SOX: Okay. Any discussion of Dr. Brook's motion to approve all three of these? In

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that case, aren't you supposed to do this?

MS. ANDERSON: This is my part. For the record, Dr. Garber is absent for this vote. And the motion is to approve all three recommendations of the Drugs Biologics and Therapeutics Panel. And those who are voting for? Those who are voting against? And those who are abstaining? It's unanimous, with the one absence.

DR. SOX: I note that we're only five minutes, and we will resume please, promptly at 1:30, because we have a very interesting discussion this afternoon.

(Luncheon recess from 12:37 to 1:38 p.m.)

DR. SOX: I would like to begin the afternoon session. We are going to spend the next hour or so reflecting on our guidelines for

evaluating diagnostic tests, specifically imaging tests, and Sean is going to lead this off. Ellen Feigal, from National Cancer Institute, is going to follow. Alan and I will make some brief unprepared comments, and then we will have a general discussion, the goal being to think about our guidelines for evaluating diagnostic tests and decide whether the results of this workshop might lead to us want to make some changes. So with that, I will turn it over

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to Sean.

DR. TUNIS: All right. Well, we decided to, you know, add this session to discuss the framework for evaluating diagnostic tests, and that hopefully, you know, people can be somewhat more interactive and controversial than they were this morning. Especially Dr. Brook, I think you really need to come to the fore to a greater extent.

(Laughter.)

DR. BROOK: You realize this is in a formal set of minutes?

DR. TUNIS: Yes.

DR. BROOK: Can I get severance pay for life from this committee?

DR. TUNIS: We will but put that through our process and let you know.

So anyway, I just wanted to give a couple minutes introduction to how we came to collaborate with the NCI and particularly Dr. Feigal on having had a workshop to address the issue of alternative frameworks for evaluating diagnostic tests. As many of you know, the existing framework that the MCAC has developed and is attempting to apply to making recommendations on diagnostic tests fundamentally works by looking at specific indications for use of

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the diagnostic tests one at a time.

So for example, we would be looking at in the imaging area, we're looking at the use of PET scanning for breast cancer, for the staging of the axillary lymph nodes, and we're looking at evidence for that specific indication and trying to make some conclusion based on the literature that directly

addressed that question. What has been pointed out as a limitation of that approach, particularly relating to imaging and oncology, is that it could potentially require a vast amount of clinical research because the number of potential clinical applications within any individual cancer are quite numerous, and you know, there's sort of the four basic categories of screening diagnosis, staging, restaging, and monitoring response to therapy, but within that there are all kinds of individual clinical applications that might even be refinements within those. So restaging colorectal cancer within the setting of a rising CEA, for example, is a specific question that one might look at separately and require a separate body of clinical research for. So one of the things that we were looking to explore was whether there were approaches to evaluation of diagnostic tests that would allow some

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sort of sensible extrapolation from clinical evidence in one particular clinical use to other clinical uses for which there is not direct scientific evidence.

And the idea would be for example, that if you knew something about the metabolic activity related to FDG of breast cancer, that might be informative if you knew then that FDG-PET was useful for restaging of breast cancer, might you also be able to make some logical conclusions about its clinical utility in monitoring responses to therapy. Those are just some examples that we're currently faced with.

As I mentioned kind of at the end of our breast cancer discussion this morning, we did for the December decision memo on PET scanning for six oncologic indications, we kind of did a quick and dirty version of this extrapolating already, which is we essentially made up a rule that said if you have clinical, good scientific proof of clinical effectiveness for a single indication within a cancer, Medicare will provide coverage for all clinical indications within that cancer except for those where there is not, where there is some evidence to suggest that it wouldn't be useful for that clinical application.

And kind of the crude notion there was

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that within a cancer there is some commonality of the biology or molecular activity related to PET and one might be able to make extrapolations that the clinical utility proven in one clinical application would be extrapolatable to others. It's by no means, that doesn't integrate seamlessly with the evidence based approach for coverage decision making or the MCAC recommendations that have been enunciated in the MCAC guidelines. And so to sort of further explore those issues we had this workshop and Ellen Feigal is going to talk a little bit about some of what came out of that workshop and then I throw the whole issue open to discussion for the committee. So with that, Ellen, I'm sure so far everyone is with us and they're completely on board.

DR. FEIGAL: And they are all awake after lunch. What I'll do then is, Sean placed things in context for you about the fact that our different agencies are working together and in addition also working with the Food and Drug Administration as

well, and what we were trying to do is brainstorm on ways to think through this process, realizing that the standard of conventional frameworks seems to be based on sound scientific and clinical principles, but to not go in the wrong direction but to balance

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this with the practical realities of conducting clinical studies in people and all the vagaries of how clinical studies need to be conducted, the particular unique problems associated with doing diagnostic studies, how it's a very complex route between a diagnostic study and the actual management that is decided on for that patient, and the fact that you have different doctors delivering the diagnostic test from the doctors who are actually personally taking care of the patient. So there are lots of complex issues to take into account as we're thinking about how to move forward and make some forward progress in this area.

So what I'll do is just give you some highlights from our workshop and then really the vast

majority of the time for discussion. And I know this goes without saying, but feel free to interrupt if you have any questions.
We're just using this as a template to focus the overhead.
Let's go to why did we even do this. As Sean went over, there were multiple reasons that we thought were important to go over. We thought that the current MCAC diagnostic guidelines as they're written requires accurate direct or empirical

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evidence for each clinical indication. The fact of the matter is there are many cancers and within each cancer there's many diagnostic clinical settings. And just to get down to the practical reality, it probably is not practical or efficient to conduct high quality evaluations for every proposed use of a diagnostic technology.
MS. RICHNER: Will we get copies of these?
DR. FEIGAL: I will send them to Janet and she could forward them.
DR. BROOK: Did you note that I wasn't the

first to interrupt? I want to note that formally for the record.

(Laughter.)

MS. RICHNER: It's always a race between you and I.

DR. BROOK: But the thing is, which is the most disruptive interruption.

DR. FEIGAL: So the overall, the purpose of this workshop was really to get together an interagency group. We wanted to get together the people who actually fund these type of scientific and clinical studies, with the agencies that regulate the approval of the products, with CMS who regulates the coverage and reimbursement for the uses of these

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products. We also wanted to get together with health care providers, with investigators who see patients, with technology developers, and see if we can at least discuss ways to think about alternative frameworks for scientifically based reproducible and understanding decision making process.

And the reason why this was really catalyzed by conversations that we've had with CMS, in that they felt that they wanted to address this in a more comprehensive way and to consider alternate ways of thinking about this issue. So we wanted to explore alternative guidelines or frameworks for evaluating diagnostic imaging that are explicit, that are practical and that are efficient, and that these guidelines or frameworks would consider several fundamental characteristics of diagnostic imaging. It may be that one size does not fit all, maybe this doesn't apply across the whole menu of diagnostic tests, but we thought there were some specific issues in diagnostic imaging that warranted further discussion and might be illustrative of other issues that you address in other areas, so this is to be thought of as an example.

DR. FERGUSON: Am I to assume this is all imaging diagnostic, not just cancer?

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DR. FEIGAL: Well, I'm focused because I'm from the National Cancer Institute, I'm focusing on

cancer. Presumably this could be illustrative of other types of diseases in which there are many different indications within a specific disease, but I'm just going to focus on the cancer issue.

Diagnostic imaging of course, these technologies have potential value for many different pathological conditions, many different diseases, and these technologies have many different specific clinical indications within each condition and for each possible indication, there are numerous other imaging or diagnostic study results for which the new modality may substitute or it may provide complementary information. I'm not telling you anything that's unique to cancer, but because I'm from the Cancer Institute I'm just going to limit my comments to the cancer issues.

We had the workshop, as I said, with people from different agencies, with people who are involved with doing technology assessment, with clinicians who actually have to see patients and make decisions when they're in their office, with

diagnostic radiologists who need to conduct these tests and interpret the results, so we had a diverse

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group in the room of about 30 to go over these issues, so we had people who had some sense of the issues we were trying to address, but also had some real experience, in the trenches experience of having to deal with patient related issues and trying to put this in the context of having some reasonable guidelines to work under.

MS. RICHNER: Did you have manufacturers at all?

DR. FEIGAL: We did not have anybody from industry at this first meeting. We thought of this sort of as a process; we wanted to get sort of our own ducks in a row to see if we could come to some points of agreement at least among ourselves, realizing that that may just be the first of several steps that may subsequently need to take place.

DR. MCNEIL: I don't understand the first bullet. Is that something you agreed was a reasonable thing to do, or is that the reason we're

here, to discuss it further?

DR. FEIGAL: This is the first time that I'm bringing this out to the group, and so why don't I go through the different points that we appeared to agree upon at the meeting. And Hal was at the meeting, Al Garber was at the meeting, Sean was at

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the meeting. I don't believe there's anybody else in this room who was at the meeting, but they can also offer their own interpretation as to our points of agreement, but this was part of a summary that we put together collaboratively and distributed to all participants at the meeting, and as far as I can tell there were no caveats to the summary. These are the consensus statements that are in the actual summary. So I'm going over these now for the first time in a more public setting.

DR. TUNIS: But just to clarify on that point, Barbara, this is really being presented as kind of raw material for you all to consider, and if the MCAC decides they really, after hearing this,

don't want to move anywhere beyond where our current guidelines are, the current MCAC framework, that's fine. This is not activity meant to supersede the authority of the MCAC to have their own guidelines and framework.

DR. MCNEIL: The reason I was asking, Sean, is that's sort of a loaded statement in my view and --

DR. FEIGAL: Well, why don't you let me before we interpret it, why don't you let me present it with some additional words besides the bullets,

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because sometimes just reading the bullets, you might come to one conclusion and so just like this morning when you were going through things, why don't you let me sort of present it and then we can discuss it. Is that all right?

DR. MCNEIL: Sure, absolutely.

DR. FEIGAL: So what we agreed on is at least to consider developing a formal approach to use modeling techniques as an adjunct or as a substitute for clinical studies evaluation diagnostic tests.

What we're saying is consider whether or not modeling might be one approach we could use to try and tackle some of the complex issues that we have to deal with, that there is a lot of evidence in one indication but a very limited amount in another clinical setting of that same cancer. Or the issue that Sean was dealing with, we may know quite a bit about breast cancer but not very much about a rare form of sarcoma. So it was trying to get a sense of -- there was at least an agreement that it was worth pursuing as an approach, I'm not saying that we can do it.

DR. BROOK: Why did you limit this to diagnostic? You have exactly the same problem on the therapeutic side.

DR. FEIGAL: Only because it's a huge

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issue and we're just trying to get our hands around something that we could handle. Also because we have developed interagency collaboration in the area of diagnostic imaging, so we were taking advantage of the fact that we already have some working

relationships with the other agencies in diagnostic imaging and so we thought it would be a good place to start.

DR. BROOK: So this is addressing the balance between modeling and clinical studies to provide evidence, is what this is about.

DR. FEIGAL: This is just one half that was discussed.

DR. BROOK: I understand that, but th overview of this is to address the issue between producing evidence by clinical studies or by modeling or combinations to advance knowledge, this is the topic that you're talking about?

DR. FEIGAL: For this one point.

DR. BROOK: For diagnostics.

DR. FEIGAL: No, for this one point of points of agreement.

DR. BROOK: It's diagnostics.

DR. FEIGAL: Correct, in diagnostics. There are other points that I'm going to get to on

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this transparency.

DR. BROOK: Okay. Can I just ask, what's the motivation for doing this, where did this come from?

DR. FEIGAL: The motivation for doing this is in the past, the way the diagnostic imaging has come into play, x-ray, CT, MRI, ultrasound, is that there has been sort of general coverage across a whole variety of diseases, a whole variety of conditions, and it's understood that there's obviously many potential problems with having a broad coverage in that regard because you may have use of the technologies in inappropriate settings. You may certainly have use in appropriate settings, but you also may have overutilization of the technology. So that's one extreme. Then what we're going to now with the current guidelines is going indication by indication by indication.

DR. BROOK: I understand, but what you said here is to use this as a coverage decision to cover tests and procedures on a specific patient indication by indication, that's what you said.

That's the major departure, not whether to use modeling or clinical evidence, but to go beyond that is that if you model this out, you would say only

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black men 60 to 69 would value from this diagnostic test and nobody else would do this, or only people that have this income or this characteristic of the tumor or this characteristic of the particular income. The really major breakthrough here is not whether you use modeling or clinical evidence, but what you're really asking is can we move the coverage decision down from we cover a therapy, you know, anyone who has breast cancer, you're covered for a mastectomy if you want, anyone that has breast cancer can get covered for a PET scan if you want it, to a very specific circumstance. That's what you're asking here, that's the question.

DR. TUNIS: I just want to say, I think it actually, if I understood it correctly, I think it's slightly that the order is in the reverse, in that coverage policy by Medicare for diagnostic technology particularly, has historically been we cover CAT

scans and we don't make a lot of distinctions, they are covered for such and such patients with these characteristics. With a more formal adoption of an evidence based approach, as manifested in recent decisions about PET, we have gotten more specific. PET is covered for colorectal cancer in the setting of a rising CEA, and the tension that this raised was

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this kind of historical balance of how Medicare used to pay for things to how we have now gone through paying for things on a very specific indication by indication basis, and the additional demands that places on clinical research that proves each indication.

So now we're exploring alternatives about are there intelligent defensible evidence based ways of going beyond that. Does that make sense?

DR. BROOK: Yeah, but the only thing I wanted to point out, there are certainly intelligible ways to do this at a doctor-patient level. That's why I asked what the motivation was; this is not at

the doctor-patient level, this is at the coverage level.

DR. FEIGAL: That's right.

DR. BROOK: And so what you're actually trying to do is move along the agenda of how, instead of having one criterion for covering CAT scans, you might have 2,000 if you produce a modeling approach, because you will, I know, because we have done this. You might have 2,000 different scenarios of which the modeling will support doing, covering for 33 percent and 50 percent, and it would have to be updated, but that's the road we're going down here. I just wanted

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to make this explicit.

DR. FEIGAL: And let me also make explicit as well that I'm not advocating one route over another, I'm not saying that this is the way I would like this committee to consider that we go. What I'm saying is from the people who were at the meeting when we were thinking about ways to intelligently discuss what the challenges were and what the problems were and what the vagaries are of doing

clinical research, how can we approach it in a rational manner, in a balanced manner. We know what the ideal is. We know what we would like every investigator to do in terms of their studies, or every sponsor to do in terms of their studies, and if we had an unlimited supply of resources, personnel and money, which nobody has, including CMS obviously, there wouldn't be any challenge, we would do that. What we're trying to do is balance the ideal with the practical realities.

And so what we are trying to think of for CMS is also a philosophical approach. It's not a right or wrong approach, is do we establish a ceiling or do we establish a floor, you know. So these are the types of issues, there is no right or wrong, it's just trying to think how can we move forward together

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in getting this done.

DR. MCNEIL: The question I had, I think may be a little bit of a follow-on to Bob's. I think the last two bullets are self explanatory and the

first one is the one on this slide that has the real meat behind it. And the issue there is, and maybe you're going to talk about it in a subsequent slide, but using modeling techniques as an adjunct or a substitute, so the issue there to me following up on what Bob said is are you using, are you proposing that the group agree, because that's what it says, points of agreement, to use modeling techniques to come to the sensitivity and specificity of a particular test for say the detection of disease, and I don't know how you do that, or were they using it to get the sensitivity and specificity of tests for a particular purpose to see if they altered management, or were they using modeling techniques to go the whole nine yards into cost effectiveness and use health outcomes, some kind of quality adjusted life year for a diagnostic test?

I think that's quite -- well first of all, I think it's probably impossible and would not be a way we would want to go.

DR. FEIGAL: As I said, I'm not an

advocate of this, I don't even know if it's possible, but there were many around the room that desired such a model to consider whether or not such a model could be developed. We didn't get into a lot of the details of the inputs, the outputs, the type of data that would need to go in here and how we would validate the model. This was the beginning of a conversation and so I can't give you a lot of details, but certainly Hal, Alan or Sean --

DR. SOX: I would suggest that Ellen plow through her transparencies without interruption and then we can come back and kind of go through it a second time, but let's see the whole picture first.

DR. FEIGAL: Let me go back to this transparency. We thought about three things from our meeting; there were lots of good discussion, people came from the technology assessment groups, from health care providers, we heard from physicians at research institutions in the field, we heard from diagnostic radiologists, we heard from all the agencies about the guidelines they use for approving

products, evidence gathered that we take into account as we're trying to fund research or support research. So all these different elements were discussed at this meeting.

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There were basically three points of agreement. One was this model that we've just spent a little bit of time discussing. The second is, you know, try to deal with things more down to earth, that we have diagnostic guidelines currently in place, to maybe consider some revisions to those current guidelines might be considered. And then three, I think we all recognize the need to support more high quality studies evaluating the clinical utility of new diagnostic tests. We all agreed that those were three important points.

These are just possible next steps just to stimulate discussion. I realize I don't need to stimulate discussion, but it was just to throw some things on the table of possible next steps that could take place. If indeed it was thought worthwhile to think about developing an analytical model, CMS would

take the lead in trying to work on the plans for developing a model, for validating the model. For example, some felt that it might be possible to develop models that incorporate existing information on a technology's technical performance, the incidence of various disease specific complications outcomes, other known information, to produce estimates of the likely clinical harms and benefits

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of an imaging procedure.

DR. BROOK: Can I ask you, where are you from, what agency.

DR. FEIGAL: National Cancer Institute.

DR. BROOK: What I'm really interested in, why is this CMS's responsibility? And I keep coming back to everything you say makes a hell of a lot of sense, the whole workshop makes sense, the recommendations make sense. What I really don't understand is, as far as I know, there is no strategic policy in the NIH to do any of this, and you've got $14 billion or $15 billion worth of money,

and you have no strategic framework for how to produce new clinical information about anything, as far as I can tell.

The bottom line I would ask -- that's on the record. The bottom line that I would ask is why should we turn this into a coverage decision and expect this agency to do it and this panel to do it, as opposed to turn this into a decision of how is the agency going to use the clinical research money it has to produce better information about when and how diagnostics tests or therapy should be used in people. And what I'm really asking is, I'm confused about why is this -- I mean, we could change our

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guidelines to do all this kind of stuff, that's easy. But I'm really confused what's happening in the government and the NIH level of a policy, or the director of the NIH, why aren't you giving him, or maybe you are, giving this briefing to him about making this happen?

DR. FEIGAL: Okay. Let me take a step back. I have been asked to be the spokesperson for

this workshop. I didn't propose that CMS do this, CMS actually proposed that they do this, okay?

DR. BROOK: With the $30,000 worth of money it has for research?

DR. FEIGAL: No. Let's take a step back, because what I'm trying to do is give you a --

DR. SOX: Bob, no more rhetorical questions for the next five minutes, please.

DR. FEIGAL: I would be very happy to give you --

DR. ALFORD-SMITH: I just want to say, I am disturbed by this. I think this is extremely relevant, I find it quite beneficial, and the way this young woman has been challenged and in my opinion harassed in some ways --

DR. BROOK: I apologize.

DR. ALFORD-SMITH: -- while she is trying

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to provide information that is ultimately going to help us in making decisions, and I would ask that we at least respect that.

DR. SOX: Go ahead, Ellen.

DR. FEIGAL: Yeah. I think that I would be very happy to describe the NIH strategic plan and the NCI strategic plan, but I don't think this body is the appropriate forum to do that. I am perfectly capable of doing that but I don't think it's appropriate. I think that we do have things that we're doing, we do have strategic areas for funding scientific research and for funding clinical studies. What we're trying to do is work with our partner agencies on a common problem, how do we take emerging technology that we think is important for patients and move it into the clinic and get clinical studies and then move it into the marketplace, where it can be disseminated and actually make an impact on the public health.

Because my sense of everybody in this room is that what we're all interested in is improving the public health. What we're trying to do is come out of our silos and try to work with our partners because we think it will be beneficial to do things together rather than to be doing things in our own

back yard. We think there is a benefit to doing that, and that was sort of the catalyst that brought our different agencies together to work on it in the area of diagnostic imaging, which is how it came to be that we are working diagnostic imaging.

So what I'm going to propose to you, and I welcome challenges, I welcome questions, because I think that is a good way to move things forward, so I don't want anybody to feel inhibited by asking questions of me, because believe me, this won't be the first time that difficult or challenging questions have been thrown my way. But I think what I do want to do is to have a productive interaction so that we can work on this collegially to make things go forward.

So this is just one possible step, is that we think about is it even feasible to develop an analytical model and what would go into it and how would you really validate it. This is an extremely complex and challenging possible next step but it's

just a step that people at the workshop thought was worth discussing in front of this body.

Now, the next possible step would be, and I'm only using CMS as an example because frankly, it's not within the mission of the NCI to determine

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coverage policy, that is within CMS's domain, so we're just sort of working together as partners to figure out the best way to do it. So the next possible next step was for CMS to work with this body to consider allowing different levels of evidence for evaluating diagnostic tests in cancer based upon whether they are high or low instance cancers.

Why use that criteria? Well, the reason why we chose that criteria is that it was something that wasn't incredibly subjective, we could tell you the incidence of different cancers, we can tell you how common it is in the population, we can tell you numbers, we can quantitate that. And since high incidence cancers affect a significant proportion of the population, we thought that diagnostic studies in these cancers would have the potential to make a

significant impact on the public health. Therefore, we thought it was probably reasonable and also feasible, because numbers of these patients is not rare, it's common, that we could do high quality studies on the common cancers.
However, we thought it was impractical to conduct the same rigorous level of studies in the lower incidence cancers. And that's not because we don't think it's important to have evidence, we're

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just trying to base this on reality, how can we really get this done and do we really want to deny using a useful technology in less common tumors only because we just don't have the infrastructure and the logical makeup to do it in every single cancer, every single indication, so it's trying to balance the science with the practical reality.
And then this would obviously involve a lot more discussion, a lot more work, but that was one proposal, is perhaps we could think of some sort of revision to the current guidelines.

And then the third issue is the issue that I think is very much in the NCI domain, the NIH domain, the NSF domain, all kinds of different funding agencies, but we need better coordination between researchers, regulators, payers and technology developers to insure the promising diagnostic technologies are adequately evaluated in an efficient and a reliable manner.

Just for your background information, the National Cancer Institute has established a whole new program in biomedical imaging. We have established funding for research going everywhere from basic with in vivo molecular and cellular imaging centers to small animal imaging research programs so that we can

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do some of the preclinical studies that will give us information to take it into humans. We have established and American College of Radiology imaging network to conduct clinical studies using imaging technologies. And then we're also now trying to work with other agencies, with industry, with whoever we need to work with to try and clarify what the

pathways are of once you do these clinical studies, how do you take it through the system, what's the type of evidence different agencies want to have. So that when the people are trying to design their studies, they know what's expected, they know the type of information people want to see.

And this as we said, requires attention to methods development, to expansion of existing research infrastructure, to funding for such studies, and also strategies for prioritizing research funding in critical areas of uncertainty. So thanks for letting me have a chance to get through what we were trying to do with this workshop, and I guess Hal and Alan are going to add their own comments, having been at the workshop themselves.

DR. SOX: We're talking ourselves out of much discussion time here but I would like to hear if Alan wants to comment on the meeting or proposal.

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DR. GARBER: Yeah. Maybe I can give a little additional context. I agree with what Ellen

said, but I probably approached it from a somewhat different point of view, so I might emphasize a few different things, and maybe this will get at some of Barbara and Bob's questions.

The fundamental issue that we have been faced with since we encountered the whole PET question is how much can you generalize when you have good studies for a few indication but not for others. At the workshop we were trying to figure out if our whole framework could accommodate an approach that would let you generalize, but only generalize where appropriate.

So the first question is, could you generalize from a study in one tumor type to another, and I think that, although I wouldn't claim there was a uniform consensus, I think the majority of people felt that you could not, you could not go from one tissue type to another, and not necessarily from one tumor size to another. So at the level of something like sensitivity and specificity, there is the feeling that no, you really couldn't generalize.

But it was also felt that it you had

sensitivity and specificity, and as you know, studies

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of test accuracy are much easier to come by than studies of effects of tests on health outcomes. If you had sensitivity and specificity for a particular indication, could you then generalize about health outcomes using some other kind of data? And that's what really I believe generated the whole discussion about modeling and I think there was a fairly broad consensus that with appropriate modeling you could take the step from test performance to health outcomes without requiring new studies to be done in every area. And of course this would have to be assessed on a case-by-case base, but the idea is that modeling could play a significant role.

The third thing about rare versus common is that we felt that as Ellen said, it's unreasonable to expect extensive studies when you're talking about a cancer that may have an incidence of a thousand cases per year in the U.S. to impose the same standards for that as for a study of colorectal

cancer or breast cancer, or prostate cancer. And so the idea was, and I don't think we reached the point of having specific language, but the idea was that we shouldn't put tests for those conditions through the same processes and same evidence criteria that we would for common ones. And we didn't want to lower

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the standards for the common ones because that's an area where we could get good information and we should encourage people to do what they can to obtain it. So the proper approach might be something like saying, we would use a standard like promising rather than adequate evidence to make decisions about those, and it would be clear that we are not endorsing the evidence at the same level as for common cancers, but we don't think HCFA should impose the same standard in deciding whether to cover.

So that was the basic thinking behind the workshop, and I think Ellen's presentation was very accurate.

DR. SOX: I'll just comment briefly that we have sort of two extremes. One is to grant

coverage for all uses of PET scanning, if it's good for one it's good for everything. On the other hand, we could require empirical studies in every indication, or we can try to find some middle ground between what some might regard as excessive permissiveness and others would certainly regard as being far too rigid. And I think the purpose of this discussion is to try to identify some promising areas to explore this middle ground.

And for purposes of discussion, I would

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like to propose and we'll see just how far it gets, to focus on this proposal that we've made, or that the summary states, which is that we focus on a particular application, namely taking modeling techniques as the basis for trying to figure out the impact of diagnostic tests like PET scanning on rare diseases and explore it, see where it takes us, and learn from it. And that therefore, we try to focus, I propose we focus our discussion on a specific instance so that we could actually go from this

meeting to a trial run, presumably using HCFA staff to try to get us off the ground, and then get a report back next time of a couple of examples of trying this modeling approach and seeing where it goes, so we can move ahead in a reasonably timely fashion.

I don't think anybody is proposing that we use modeling techniques to estimate test performance. What I think we're talking about is modeling techniques to estimate the impact of diagnostic test performance on health outcomes, basically using the model that we've already got. So Barbara, I think you had your hand up first, and then John.

DR. MCNEIL: I'm glad to hear you say that, Hal, because I think your remarks aren't quite

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equal to what is in the summary here and I didn't quite get that from Ellen's talk. It would seem to me that at the very least for high volume tumors, whatever that means, high incidence, whatever, we absolutely positively have to have critical data at the first step of the process. There is no way we

can model sensitivity and specificity, it just can't be done. So I think that should be put forth as a given in paragraph 1. We never said we were going to model sensitivity and specificity, and we want to get clinical studies to do that.

The issue is therefore twofold. The first of those twofold is, do we think we can take the sensitivity and specificity date that we have for high volume tumors and then somehow or other with some model, and I don't know what model means in this circumstance, translate those to low incidence tumors. No?

DR. GARBER: That was not the intent.

DR. MCNEIL: Well, okay. Then the other one would be to say to take the information we have on high volume tumors on sensitivity and specificity, and then to roll out a full model that would end up with something like cost effectiveness, or cost per quality adjusted life year.

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DR. GARBER: No, just effect on outcomes.

DR. MCNEIL: So just the denominator, fine. So to take the initial data for the high volume tumors or for the low volume tumors? Because I could imagine if you have a matrix and you can fill in the cells in several different ways, and this is what I don't understand.

DR. GARBER: Could I explain what I think was intended? This could, you may or may not think this is a reasonable way to go, but the idea is that modeling could be used broadly, not just high volume versus low volume, to link test accuracy data to final health outcomes. And there could be, we didn't delve into what types of information you would need to develop those links, but obviously it would be different in different clinical situations. That's really a separate question from the high versus low volume. In other words, even for high volume tumors, we were not saying you would necessarily have to have randomized trials to look at effects on mortality and so on from using the diagnostic tests, we would use modeling to link accuracy. But the standards even for test accuracy

might be different for low volume than for high volume tumors. The expectations we have about study

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design, sample size and so on would obviously be different for a high volume than for a low volume tumor.

There was never ever any idea that you would model sensitivity and specificity. That has to be data from direct measurements.

DR. SOX: But you would model consequences.

DR. GARBER: Yeah, you would model consequences. I mean, one of the questions is, in every situation you want to know for example if you change the probability of disease somewhat by using the test, is it going to actually under optimal circumstances affect management or change outcomes and if the answer is no, within the realm of sensitivity and specificity you see in the data, the answer is no, then the test is not useful. And conversely, it might be very useful, and that's how

modeling can be helpful.

DR. MCNEIL: So would the modeling here, Alan, be modeling -- so we've got the sensitivity and specificity for whatever the tumor is, and in the past this group has said if the sensitivity and specificity look like they will improve health outcomes in the way we talked about today, perhaps

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just by changing management so that you upstage or you downstage, that's enough. This would go beyond that?

DR. GARBER: Well, you know, the panels have to decide what's adequate evidence of health benefit and I don't think we can write that into any set of guidelines. But the idea is that health outcome has to be improved. Now if they think that a change in management is an adequate proxy, if they are willing to believe that a change in management will lead to a change in health outcomes, that answers the problem, that's all the model needs to do. Our expectation though, is that usually if you're going to model the change in management you

should go all the way to modeling effects on final outcomes, but that's really for the panels to determine in my opinion.

DR. TUNIS: I just wanted to -- Alan, when you say we never anticipated or suggested modeling sensitivity or specificity, I just wanted to make sure that you know, one of our intentions was to explore the possibility that you could use sensitivity and specificity information that you might have gotten from a study on initial staging of breast cancer, and use that same sensitivity and

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specificity information in looking at the clinical utility of monitoring response to therapy for breast cancer. And I just want to make sure whether you have, do or don't have misgivings about that kind of extrapolation, where you haven't done a new clinical study looking specifically at sensitivity and specificity in a monitoring study as opposed to being able to borrow it from a clinical study you did on initial staging.

DR. GARBER: Well, this is really a good question, and you know, I don't think the Executive Committee or any other group can come up with a set of rules that can be directly applied in every situation. But we had a discussion like that at the meeting which I'm sure is why Sean was bringing it up, and I think we agreed that you couldn't extrapolate from one tumor type to another. It's maybe less clear if you can, if results for primary tumor would apply also to recurrent tumor, if the site matters, if the size matters, but there are questions about that, and there will be at some level no matter what we say here, there is going to have to be a judgment call.

If it's in the axilla is it going to, can you assume the same sensitivity and specificity in

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the abdomen or the lung or something, and there we might have to deal with it on a case-by-case basis. But in discussion, there seemed to be a lot of skepticism about generalizing from one site to another and from one indication to another even for

the same tumor type because for example, the metabolic activity in a recurrent tumor might not be the same as in the original primary, so you wouldn't necessarily expect PET to have the same sensitivity in both situations. So, I don't think we can get to that level of detail but clearly there will have to be a discussion about whether you can extrapolate from one study to a slightly different clinical setting.

DR. SOX: Let's see, Daisy.

DR. ALFORD-SMITH: I didn't have one.

DR. SOX: I'm sorry, Leslie.

DR. FRANCIS: As I understand it, all that we're being asked to look at now is does it make sense to explore the possibility of developing models sometimes, either to supplement or to replace the wonderful randomized clinical trial which we're not going to have all the time, right? And the answer to that seems really easy, of course. What I don't think we can really talk about here is the adequacy

of any particular model which we're of course always going to have to talk about anytime there is a suggestion that a model ought to substitute for the actual clinical trial. Some models will be good models and some models won't be good models, and that's going to have to be discussed.

Now I don't know whether the group got into some more general guidelines about when models are likely to be good, or whether all they did, what I heard you talking about was that there are sometimes when we have antecedent reason to think that we're not going to have the randomized clinical trials, so we would make people wait too long or wait forever if we insisted on that, so those are the areas where you are going to want to really start looking for models because we're not going to get the -- that's why the, it's not that you think models are necessarily likely to be better with low incidence cancers, it's that you think that we're more likely to have to rely on them if we are going to do anything at all because we are not going to have the data from the study.

DR. FEIGAL: What I'm getting is the issue of sort of the matrix approach where you have the cancer and you have an indication, and you have to

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have the data in each box, and what I'm saying is some technologies, as you know, the process that it's measuring -- and we're getting into obviously nonanatomic imaging. There's going to be functional imaging, there's going to be imaging based on molecular characteristics of tumors that are going to probably change how we characterize tumors, how we classify them even, and these processes are going to go across tumors, these molecular characteristics that we're looking at. So all I'm saying is that we have to think creatively, that our standard frameworks may not hold for this new era that we're going into, and it would be nice to be prepared for that new era by thinking about how we are going to evaluate those types of technologies.

But to answer your specific question about the model, it may be we have some information about

the avidity of an imaging agent in different tissues, you know, in breast tissue and liver, in tumor versus normal, and is there a way to use that information in deciding whether or not that imaging modality might be useful. So it's to go beyond the traditional clinical study and think about all the different types of studies you might do that might provide you with useful information in making your decision.

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It's a very hard issue to really get your hands around and it's a very challenging issue to think about how you would really approach it, but it's just trying to tell you, you may have certain elements of information but it may not be the euboxic type or easy to look at, that may not be available.

DR. SOX: Next, I think John has been waiting.

DR. FERGUSON: Are there any examples of modeling being predictive of outcomes in the diagnostic field, are there some?

DR. GARBER: You mean where it has been validated?

DR. FERGUSON: Where it has been validated.

DR. MCNEIL: There aren't too many good models out there, are there, Alan? There's one and I don't know if it -- I mean, that a good example to use as the point, because of a situation where the impact of a particular diagnostic on therapy is quite clear-cut and the impact of therapy on outcomes is kind of like penicillin, so I don't think anybody would think it necessary.

MS. RICHNER: There have been several modeling examples in IVIS and other technologies, but

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I mean, that's not cancer. Is that kind of what you're looking at in terms of what has been done before?

DR. GARBER: No. The question is validating diagnostic tests, I think it John's question.

DR. FERGUSON: I just wondered if there was an example.

DR. GARBER: Have the models been validated against randomized trials, and if you look at the whole group of studies, they are almost all therapeutic studies.

DR. MCNEIL: Right, that's the problem. And the problem there is the fact that you can't match up, if you're doing a decision analysis and every single node you have to know, particularly for cancer, you would have to know the impact of a false positive and a false negative decision, and the clinical trial data --

DR. SOX: Yeah, it might be doable for screening tests where you have randomized trials of breast cancer that allow you to make inferences about the impact on longevity, but I don't know that anybody has actually done that.

So let's go on. Bob.

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DR. BROOK: I would just like to put a comment on the table that I agree with the thought behind this, but I'm not sure where the proper place to use it is. Let me go back to the beginning.

There are three ways that you could produce information. One is what we've labeled empirical science, one is modeling or analytic techniques, and one is sophisticated consensus and clinical judgments. All three have a place in trying to figure out what to do with a patient and when to make a coverage decision.

We have done this in multiple different ways and have actually done a lot of validity studies on some of this stuff. If you take a diagnostic test like colonoscopy and ask the question of how often it should be done, how frequently, on whom it should be done, when it should be done, you wind up with thousands of possible scenarios that this can be used on, that the individual doctor and patient need to make a decision of what to do.

We've tried to work with David Eddy about how you model some of this out at a higher level, how do you do some of this modeling to figure out how to use the current data. Why I was a little cynical is that we have been stuck with that nobody really wants

to put together the kind of detailed sophisticated observational longitudinal databases that would allow you to do some of this work. What's obvious from the work, the studies that have been reported here and the ones that have been referred to us, is I'm not sure modeling will help us much because the data is so deficient to go forward with. And what I am suggesting, or what I wanted to suggest is that we do some push back and we really do ask the NIH the question that HCFA is going to be faced with making coverage, or CMS, coverage decisions. We're going to have scarcer resources in the future given all of these thousands of things. There are a whole slew of proposals on the table of what needs to be done in terms of long-term high quality observational databases that will have sufficient data in that they could be used in conjunction with randomized controlled trials to produce the input to models that would help up us make all of these decisions from the patient-doctor relationship to the coverage decision. There is no coordinated federal policy on

figuring out what to do there. In Washington in two weeks, this group that Kantor has put together under the aegis of AHRQ is going to meet about health information issues, and the same sort of questions

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are being raised. That's all I'm saying.

In terms of this, I would argue let's try it, I would argue that in most decisions that have come our way at this moment, the data will not be sufficient to help us much with the modeling, and that we will have to ask experts to provide the estimates of the points that need to be put into models. That's where we got stuck. You break down the way you use experts. You can't find the real data and you would have to have experts extrapolate it, just like we were trying to do around the table, which is fine. In a formal model that may be very useful, and we ought to try it.

I would also call your attention to this guy's work with the NIH consensus conferences. He tried modeling and it was a disaster, he probably

repressed it, but Parker came down to model the whole use of estrogens for the NIH consensus conference in terms of the use of estrogens and risks and benefits to a group of esteemed clinicians in one of the famous NIH conferences, and I won't go beyond that because we're on the record here, but it was a two-day tour deforce or more than that, of trying to figure out how to use formal modeling to come up with a consensus conference judgment. It may not be a

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coverage judgment but it's similar, in terms of what to do.

So I'm all for this, I'm all for it, but I think the partnership is a two-way partnership here. The NIH is going to need to change the way it produces the raw clinical information to be used if we are going to be able to provide sufficient model techniques to do this.

DR. SOX: But CMS also has some obligations to organize data sets that could serve this function if we're really going to do it.

DR. BROOK: They would need new, I believe

it's the case that they would need new monies and legislative authority. I mean, I wasn't being facetious. I do not believe this can be done on the research and development budgets that CMS has traditionally gotten. We can propose that CMS go back into the OMB in the budgeting process to get the funds to do that, but given their budget, Hal, it's hard for me to believe that it's realistic to suggest that this is an option.

DR. SOX: I was really referring not so much having an army of decision modelists so much as making sure that HCFA data sets would serve the purpose that you've described for providing numbers

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that can be used for decision model work.

DR. BROOK: One of the options would be to switch the pro program around to make its major function to collect these kind of clinical observation data sets. I mean, there's lot of ways, but we're going beyond, I fear we're going beyond our mission here in terms of what we want to do. The

fundamental thing is to reorient. What we're running into is that the government has not had a serious analytical framework of how it's going to invest federal money and providing new clinical information so that it will be useful to both people that have to decide whether to pay for the services and people that have to decide what to do between the doctor and patient. There is no formal policy there, and anything we can do to push that along, if we do the models and find that they are not useful, let's do it, so I would vote to do this.

DR. SOX: I would like people, as we're going to have to wrap this up in the next five to seven minutes, so if you could focus your questions on why we shouldn't do this or sort of important caveats about what to be careful when we go ahead and are doing it, because I am sensing a reasonable amount of momentum that we should get our feet wet

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and try it out. So I think, Barbara.

DR. MCNEIL: I don't want to slow down the train, but I still don't know what this is. It seems

really vague for a group that has been knee deep in precision for so long and what I would prefer to see before we make a decision to go forward is that somebody, and it may be the people who were at the conference who are in this room, give me a much better understanding of the scope of modeling in a way that I can understand. Because when we talk about modeling outcomes, I just don't know -- I know what it means, I can translate the words, but operationally I just don't get it. So personally I can't vote for this unless I have more specificity to the scope of modeling.

DR. SOX: Alan, I think you're next, and then Randel.

DR. GARBER: My comment touches on Barbara's point about getting specifics here, and I just wanted to turn to the issue of how the guidelines that we now have would need to be changed, and I actually didn't see this as a call for significant change in the guidelines because we actually already have language in there that

basically says do modeling.

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The area where there is a change, though, is on the rare disease, and we had some language but it was very limited, and what we might want to discuss in particular is do we want to say that there would be a separate category for rare diseases, or rare circumstances I should say, to on one hand say that we can't use the usual criteria but on the other hand say that some standards should apply and to try to refine them. That would be change, so the question is whether the Executive Committee feels that this is something for which a writing subcommittee again should draft some language and then bring it to the Executive Committee or not.

DR. SOX: I would like to say yes, that we will see how we will feel after we have tried to do this for a few examples and get our feet wet to see whether it's feasible.

DR. GARBER: In terms of linking to outcomes, by the way, I presented a study that's done by a colleague of mine at the workshop that

illustrated what we had in mind and you know, once that's available in a form that can be circulated, I think we could pull lots of examples actually, to show what we would mean by the modeling effort.

DR. SOX: In a way there is an example in

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our own guidelines showing post-test probabilities and then talking about what threshold you might consider to be a reasonable one for doing nothing and therefore changing management as a result of a negative test. So, do you want to come right back, Barbara?

DR. MCNEIL: I still don't get it, Hal, to be perfectly honest. Either we're tweaking slightly the written guidelines in the manner that Alan said, or we really are embarking on something different. And if it's something different than tweaking the rare disease guidelines --

DR. BROOK: The only thing different that we're doing is we're saying that we would like to see if not a parallel process, but the next time a

question or some other question comes by, that the panel does something more than just sit around in the room and look at the evidence tables, that there might be a modeling process that is done prior to that meeting, which we've already agreed would be useful, that might help make the process a more rational decision, and we don't know yet and so we have to figure out the issue, and that's all we're saying. There has been no process that we've done, that we've done what John did 20 years ago in the NIH

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consensus conference. There have been 20 years that passed, we've got two of the best modelers in the world sitting across the table, let's take a whack at seeing whether they can be helpful in making this process better.

DR. MCNEIL: If that's what it is, let's try a --

DR. BROOK: Of course it is.

DR. MCNEIL: That's not what I heard. I heard something grander than that, but that's fine.

DR. SOX: Barbara, I think it could be the

beginning of something considerably grander and as I proposed in my earlier remarks, let's take this specific instance and try to see if we can take data from a common tumor and apply it to a less common tumor and see what we learn from that by way of advice to us as about to how to proceed, as an exercise. But later on, if we, you know, a year from now we might say hey, this is really helping us, we could do it in some other instances that aren't so rare tumors.

I think it's really important to recognize that we shouldn't let the perfect be the enemy of the good in the process of technology evaluation, because otherwise we may never get off the ground.

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MS. RICHNER: When you say something grander, what do you mean? I mean, are you essentially saying that if we have a technology like PET that was referred to us, then we would take that breast cancer PET indication, you would send it off to whoever, you or Alan, to model that, and then come

back to us then with the answer, with the synthesis of the literature? How is this going to work? I mean, this is like a major deal.

DR. BROOK: I think we should not make it a major deal. I think we should vote on something like we can give the chair the discretion, we would like to suggest that we follow up on this report and that when the opportunity comes around, that we actively try to seek the resources to figure out whether analytical and modeling work will help the panels do their work better, and they report back to us so we can learn from this and change our process. That's all that's being asked.

DR. SOX: So if anybody objects to us taking this step, now is the time to do it.

DR. GARBER: Hal, I just wanted to clarify whether I understood you correctly because I didn't quite have the same understanding about extrapolating from common to rare tumors. I think that there was

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consensus that you could not extrapolate say from colorectal cancer to chondrosarcoma, about the

accuracy of the test, and so the intent is not to say that you would model from a common tumor to rare one in that sense. I think the main role of modeling is to close the gap, and that's why it's not really changed in our guidelines, to close the gap from test accuracy data which you often have, to health outcomes where you rarely have direct measures. And we are not talking about extrapolating from one tumor type to another, at least when it comes to PET scanning, because all of the people at the conference agreed that you could not infer that the sensitivity and specificity in one cell type confirms results for another.

DR. BROOK: I think the issue here is that the process that we would like to follow, if we agree, is one where we go through our normal process as we're going through it, and we begin to supplement it with questions. Hal's question may be perfectly legitimate, you may be right. We will never answer this if we don't actually try out some things and see how it works. And the function of the group to me,

since we have not other function, to sort of try to figure out the combination between how these things

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work and how it changes the process, and we'll learn as we go along.

And I'm not scared about -- I mean, you've got the world's expertise on this committee, we might as well try it out. All we have to is convince the CMS people to provide the money to do it.

DR. SOX: So what Bob is saying, this is an opportunity for leadership.

DR. BROOK: This is an opportunity to do some out of the box work. You don't need to worry about the results yet, Barbara, until after we see what they are.

DR. MCNEIL: No, I don't care what the results show, Bob. I just want to make sure I understand what we're doing, I really do want to make sure I absolutely understand.

DR. BROOK: Hal wants to extrapolate common data to data; let's see if we can do that. Alan wants to extrapolate diagnostic sensitivity to

health outcomes data. Some other person may want to extrapolate from whites to blacks, from young to the old. There are all sorts of uses for modeling that we have not, we don't do.

DR. MCNEIL: So my question is, I understand that clearly, I understand the scope of

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potential modeling activities. I just want to know what it is we're voting on, and I can envision two things we're voting on right now. One is, we are putting up a little flag that's a trial balloon, and the flag might be, let's take the PET example that we talked about where we voted not unanimously in our subcommittee for PET as an adjunct to. Now, are we saying that that is a just terrific example to take those data and model them out and find out what the impact of outcomes is, and is that a trial that we want to explore? That's one possibility.

Or, are we saying let's take Alzheimer's disease, which is coming up in January, let's look at that and not look at it within the framework that we

looked at PET but rather look at the use of PET and SPECT on outcomes in Alzheimer's disease. Or are we saying in this vote, this is just a vote now, because this is the next step.

Is the next step a taxonomy of the kinds of things that we might do. I used to model in my day so I have nothing against modeling. I think I know the limitations pretty well. I just want to know what it is we're voting for, and I don't.

DR. SOX: Time is late and I would like to suggest that the committee basically say to Sean, you

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know, come up with something by our next meeting, get the people on the committee involved who have real expertise to help define a good question that we all agree that if we got an answer, we could take it reasonably seriously. And so I'm sure he will be scheduling a conference call that you would be involved in, Barbara.

I think we need kind of a push in that direction from the committee and then I'm sure that Sean and others will use us to try to make sure that

it's not a waste of time. Would that feel okay?
DR. MCNEIL: That would be fine with me because I would feel like I'm getting more information before making a decision.
DR. BROOK: Can we move that?
DR. SOX: Somebody can, I can't.
DR. BROOK: So move.
DR. MCNEIL: You moved it, I'll second.
DR. SOX: Wade, you have the opportunity for comment.
DR. AUBRY: I just want to make a brief comment. First of all, I think there are other examples of Medicare coverage in which diagnostic tests have been considered per indication. I think magnetic resonance angiography us an example of that.

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The other point is I agree in general with the discussion. I would like to see this developed further. One concern I have is that I see that there may be some overlap between modeling, particularly from sensitivity and specificity to outcomes, and

forecasting, which would be based on determination of outcomes based on estimates by experts, and there are different ways of forecasting, but it seems to me that we don't really want to be doing forecasting, and I see that as somewhat of a pitfall.

And I also would like to say that I think the greatest need that I perceive is in the rare tumor area or in the rare disease, in which you are never going to have enough data. And this came up at our Blue Cross/Blue Shield TEC panel all the time, particularly for therapeutics, say for childhood cancer is a very good example of that. So I see that as a greater need than for more common diseases in which we really should, I think, expect data and good studies.

DR. SOX: Anything else before we come to the end of this discussion?

DR. GARBER: Well, I think on that point, Hal, your proposal has to do with modeling, and I think we ought to keep the issue of the rare diseases

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separate. I reiterate what I said before, modeling I

don't think requires any significant change in our existing document. The rare diseases potentially does. Now I don't if Sean wants to approach this as one package or to separate those issues, but to my mind anyway, and I think this reflects the discussion at the meeting, the rare diseases was not primarily an issue of modeling, it's would you then use different standards of evidence. So I think it's very important for us to keep these separate, and I would just like to maybe add as a friendly amendment to your proposal that we explore having some language to deal with the rare conditions in our guidelines document.

DR. SOX: Okay. Good. Anything else? In that case, we are going to move on to a series of relatively short items that come under the heading of other MCAC business, so Sean, that seems to be your cue.

DR. TUNIS: While I'm sure everyone is now running somewhat out of steam, which is probably good, so I just wanted to raise a couple of issues,

and I don't think we will go all the way to 3:30, or hopefully not.

The first issue is, several MCAC members

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have brought to my attention that they have been receiving some communication from technology advocates around particular issues, and I just wanted to make sure everyone understands that you are under no obligation as an MCAC member to take any particular phone calls or respond to any particular letters promoting a particular position on your part. You are only special government employees when you're here, as far as I know, and so you are certainly welcome to take those phone calls and talk to those folks, but you are under no obligation to do so. That obviously falls -- and one of the things you can certainly do when folks want to provide you some information on a particular issue that's before you is, you know, advise them to provide the information to CMS and we will be sure that the MCAC committee members all get the information if it's going to be relevant to the

decision. You know, it to some degree borders on a violation of our open public process to be having individuals have information that not the entire committee or the public doesn't have access to.

MS. RICHNER: Well, when you go back to the charter and how this all originated, one of the ways you can easily facilitate this is simply say go

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to your industry representative if that's the case, if it's an industry person that's coming to you with information. Then the industry rep has the responsibility of coming to the committee with the information. Then the other possibility is to just simply refer that person to CMS, CMS then is supposed to disseminate the information among all the committee members. That's at least the process that the industry is supposed to observe.

DR. TUNIS: Right, and that generally -- again, you're allowed to talk to anyone you want to, but generally again, you are under no obligation and the thing you should do is just refer them back

through us.
DR. BROOK: That's very different from what you told us when we began.
DR. TUNIS: From what I told you?
DR. BROOK: We were explicitly instructed not to talk to people while we were involved in making those decisions, and to refer those -- remember, if we had the conversations, that two of us would be on the phone at a time.
DR. GARBER: I think that predated Sean.
DR. BROOK: I know it predated Sean, but it was part of the process. It predated you. So now

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we can talk to anyone, but just be careful is the rule?
DR. TUNIS: Well, no. I'm just saying that we can't make rules about, you all have lives outside of here and in many cases they overlap some of the issues that you're dealing with. So you know, I can't tell Frank Papatheofanis never to talk to another PET manufacturer, but he's not obligated to talk to anyone he doesn't feel like talking to. So

that's the main thing.
On the issue, of really the only topic so far that we are fairly sure, well, we know is going to a panel, will be the neuroimaging for suspected dementia which is, as I mentioned earlier, going January 10th to the Diagnostic Imaging panel.
DR. FERGUSON: Is that neuroimaging or just PET?
DR. TUNIS: Well, I don't know if Deb Zarin is here, but I believe it's all neuroimaging, and in fact that is being done partly as you all were involved in discussing this at your last meeting, but that is being done in part as a modeling exercise. And we are trying to take on functional MRI, SPECT, as well as CT and MRI structural imaging. We're just looking for other ways to get in trouble and we

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thought this one would accomplish it.
(Laughter.)
The PET for myocardial viability, we had intended to also go to a panel and we're discussing

that internally, and it's not 100 percent clear that would go to a panel, although it probably will. That sort of gets into a couple of other broader issues that I would just like to have your input on, both of these. One relates to some additional discussion on criteria by which CMS decides to refer things to the panel. We have had some general criteria which basically has gone to the tune of complex and/or controversial issues, which gives us a whole lot of latitude. But while we are in the middle of writing a new Federal Register notice describing our process, it would be interesting to hear your input on whether that can be fleshed out a bit more, and so we will get to that. The other thing I wanted to just run by you is some thoughts that we've had internally about reconfiguring the MCAC panels in terms of number and composition, and these ideas are at a very early stage and we wanted to make sure we got your input at and early point. So maybe then, let me just sort of throw

that out and we can talk about the two things together, which is basically we're thinking of collapsing the six panels into three panels, partly from a perspective of tractability, partly because of the infrequency with which some of the panels have been meeting. And it would be, I don't have the exact list here but there's some matching in terms of DME would go into the Medical Devices panel, or they would be merged. I believe we were thinking of merging the Drugs, Biologics and Therapeutics with the Medical and Surgical panel, and then I believe the Diagnostic Imaging and the Laboratory into sort of a diagnostics panel.

What we would do with the membership is that we would keep both of the chairs and the vice chairs, so we would actually have co-chairs and co-vice chairs for each of these panels; we don't want to kick out any chairs and vice chairs. But for any given meeting of a panel, there would only be one chair and one vice chair at a given panel meeting. For all other panel meetings, there would be no

standing assignments of panel members to any of these panels; the rest of the MCAC would be a large undifferentiated pool of experts which we would try to balance somewhat according to the distribution of

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issues that tend to come before use, so probably more cardiologists than herpetologists, and -- hepatologists.

(Laughter.)

Yeah, we have very few snake related issues.

And then for whatever topic then that comes up that we decided will be referred to a panel, we will actually constitute that panel by overweighting it with the people who have an expertise in that clinical area. So that's basically -- you all would still be the Executive Committee, maintain your chair and vice chair assigned to your panels, although they would be these reconstituted panels, and then a big pool of MCAC members, who we would call upon and form a 15-member panel for each given meeting.

And then the only other thing I would say is that we are also intending to increase the number of formally trained methodologists on any given panel, so probably have somewhere between two and four card carrying methodologists at each panel meeting, as well as you know, four to six people with clinical experience with an active clinical practice related to the area that we're addressing, and then

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fill out the panel with other folks.
And I think the only thing that I missed is that the consumer and industry representatives would also stay with their panels as standing members and would not be part of this floating pool so to speak.
DR. FRANCIS: Is there any risk that you might be perceived as having a bias in how you select panels if it's so much more open.
DR. TUNIS: We don't get generally accused of that, no.
DR. FRANCIS: Well, if it's a huge pool of

everybody on the MCAC, rather than everybody on Drugs, Biologics and Therapeutics, I just want to raise that because that's the outside public perception or concern.

DR. TUNIS: I think that's a concern and a potential drawback to this approach, and you know, it would probably obligate us to come up with some explicit process for how we identify which panel members will actually go on a panel, although I hoped that we could accomplish this by virtue of selecting, you know, MCAC members fairly well, and those with frank conflicts of interest wouldn't be part of the panel and we would be okay, but presumably it would

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be controversial too.

DR. SOX: There is another concern with drawing randomly from a pool of experts and that is you won't evolve the group skills of a panel to the point where they work efficiently throughout the whole day. We all know there's a tendency for people who don't know each other to have a little bit of difficulty really meshing at the beginning of a

meeting. Sometimes the whole morning goes by with people just kind of trying to establish themselves as individuals, and one of the advantages of this group is that we've worked together a lot and although it might not appear that way to outside people, the fact is that we really hum, even though it looks a little disorganized.

DR. TUNIS: Yeah, I think to some degree what that's going to be counterbalanced by, that's another downside, but what seems to be a limitation of some of the panel meetings we have had are the small number of folks who have real content expertise in that area who have been able to really engage the meat of the content of the issue. We've tried to fix that a little bit by adding some nonvoting experts to a panel, but we've come to rely tremendously on the folks who happen to show up who have, you know,

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content expertise, and we really use them, possibly more extensively than we should, given that they're usually there for a reason, which is you know, to

support the technology.
DR. AUBRY: I was just going to make that point. It seems to me that you have already moved some people around on panels, had temporary voting members or guests to round out panels, so in some sense you're doing some of this already. So I don't have any problem with the idea.
I do think what's probably going to happen as a practical matter is that there are some people who are probably going to serve very rarely, who won't have gone to a meeting for a year or two or something, but some of that is happening now.
DR. SOX: Well, the only comment I would like to make is defining of questions, and you probably made a slip when you said you would pull this group of people together just for the meeting. In fact, I'm sure what you meant was that you are going to pull them together for the whole assignment, and we've talked today a fair amount about the panel basically deciding the questions were all wrong, not having them buy into the questions. You have been engaging the panel chairs and vice chairs in trying

to formulate those questions, and I just urge you to adopt a process whereby all the members of the committee are brought in at an early stage, either by having two meetings of the committee, the first of which is to get the problem scoped out and define the questions and talk it through, or at the very least have a conference call at which time you do that, to minimize the chance that you're going to have more of this just throw out the original questions and improvise on the spot during the meeting, which I don't think is such a good idea.

Bob.

DR. BROOK: I have one other question.

I'm concerned with the process of getting together that minimizes making wrong decisions, and the way we have done this process and the way you're planning on doing it is to emphasize more and more getting over this evidence hurdle. We discussed at this group recommendations where things have been approved for coverage and not things that haven't been approved.

I mean, it would be interesting to go through the actual time we spent to see if indeed our group process is that we concentrate more on trying to overturn approved things as opposed to go back and look at things that haven't been approved and try to

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approve them.
From the panel process, you're now adding methodologists to it. The methodologist's role will be probably even more not to be constructive in terms of finding evidence out of you know, slop, but to basically take evidence that might be there and you know, provide caveats about why it's not as good as it really looked by the first pass, when somebody with less methodologic ability looked at it. Now I'm hypothesizing, these are all hypotheses, I don't know whether they're true, but I do believe we need to look at our decisions we have made, our recommendations, look to which ones you've taken, and have some evaluative process that we are doing either what you call a post-marketing surveillance or something, to make sure we're doing anybody any good

in this country. So that if somebody two years from now asks you to testify to what good have we done, there might be something to show them one way or the other about what we've done, and I think that can be set up to make that happen.

I'm really concerned that we don't know the answer to the question of, are the things that we're doing things that really are useful to do.

MS. RICHNER: In terms of your

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restructuring the panels, regrouping them into three, et cetera, you know, we did prepare a process and guidelines where there were some things that we recommended that be done, like for instance, the panel must explain its conclusions in writing and all that type of thing, and so far I haven't seen any evidence of any of that, and I was just wondering if we actually asked the panels to do what we said they were supposed to, maybe some of these problems wouldn't have occurred, especially like today with what happened this morning.

DR. BROOK: Yeah. For the record, could we have somebody look at guidelines that we implemented, and try to sort of see the correspondence between what happened on the last two presentations and see what we need to do not to beat people up but to improve the process, and how do we involve us in doing that, because that would be very useful.

MS. RICHNER: And also the questions issue, we did address that. Remember, there was a process where we were supposed to post the questions on the web, there was supposed to be a whole process for determining those questions, so there is a process in place that we haven't really done yet, so

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maybe if we started following what we wrote, we worked hard on this, that may solve some of our problems.

So the consolidation of the panels, including the methodologists and all that kind of thing, I'm also concerned about how that would work with this and what we've described.

DR. SOX: I have a paucity of experience to relate. The automatic blood pressure monitoring panel chair, which is me, I was asked I think along with the vice chair, to review what HCFA now CMS wrote up as well as its actual coverage decision, and to give input into the fine shadings of the meanings and so forth, which I considered to be a really positive step. So there's at least one things that's happened in one instance that was good. Tom.

DR. HOLOHAN: I think we're making too much of a minor point. The reason that at least the drugs panel changed the question was in the main a result of the fact that they saw at that meeting for the first time the FDA approval letter with a specification of serum levels and the commentary that you could treat serum levels with this drug, but you could not anticipate changes in the signs and symptoms alleged to be amenable to carnitine therapy.

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That had never been seen by anybody on the panel prior to that day.

That made the single biggest difference in that panel deciding that well, in fact none of the data we've heard and most of the testimony has never addressed actually what is carnitine deficiency. There is no way you are going to change that if those events occur. That wasn't CMS's fault, that was FDA. They had intended, as I understand, to be there to testify, changed their mind at the last minute and provided a single sheet of paper.

DR. BROOK: All we're asking is if we are going to do this correctly, the transparency of the process, I mean, stop the issue of blame, it's the transparency of the process. I mean, what Hal told us, we don't know. What you just told us, we don't know. And the question is, maybe there is something between 500 pages of materials this high and three-and-a-half pages that would be useful to help understand where we're going. That's all I'm saying. I mean, that would be a wonderful thing to say, but we got the questions on the day of the meeting, we saw something, and based on what we saw, we had to change the question. Three sentences.

DR. TUNIS: I think the point is taken

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from today of highlighting yet again the importance of not only the questions themselves but the process by which the questions are derived, and I think we will after this meeting go back, look at process of documenting them. We are evolving an entire set of standard operating procedures for every element of the coverage process, which are getting towards a usable form, and the procedures that we use for the MCAC process is one part of those, so I think we will be probably more faithful to that document in future meetings.

And we probably at this point want to come close to wrapping up, unless anyone wanted to say any burning thing about criteria for referral.

MS. RICHNER: Criteria for referral is an important one that, can you at least bring up now what you're thinking about in terms of what questions or issues you're bringing to the panels.

DR. TUNIS: Again, we haven't gone a lot

beyond the issue of things for which the evidence is complex and at least, not obviously conclusive in one direction or another. So we don't bring things to the panel where the body of scientific evidence is fairly simple and straightforward and you know, drives you to a fairly natural conclusion. So

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evidence that's a little more complex, not clearly pointing in one direction or another, and where there are kind of overarching issues of controversy. For instance, PET for Alzheimer's diseases, where there's issues of prognostic information, the value of that, and issues of the effectiveness of treatment, where we just simply don't want to make all of those kind of judgments internally, without a whole lot of opportunity for public hearing.

MS. RICHNER: It just seems like the panel over the last year has been PETs are us, it's just PET, PET, PET every single time. It seems like it's a little -- what else are we going to talk about other than PET?

DR. SOX: Well, we're at the end of the

meeting, and only one of our members has gone yet. Don't stand up please, because Janet has to dismiss us.

MS. ANDERSON: Now you're all at my mercy, so let's wrap this up.

I want to invite everyone for continuing information to visit the CMS web site which is still www.hcfa.gov\coverage., or simply www.hcfa.gov, and click on the coverage process.

To conclude today's session, would someone

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please move that the meeting be adjourned.

DR. ALFORD-SMITH: So move.

DR. MURRAY: Second.

MS. ANDERSON: Thank you so much, the meeting is adjourned.

(Whereupon, the meeting adjourned at 3:16 p.m.)